Volume XX SECTION ONE Number 5

JUN 17 1959

MEDICAL LIBRARY
HISTORICAL BUILDING
DES MOINES, IOWA

DISEASES OF THE NERVOUS SYSTEM

A Practical Journal on Psychiatry and Neurology

MAY
1959

(CONTENTS ON PAGE 194)

Published monthly by PHYSICIANS POSTGRADUATE PRESS, 277 Broadway, New York 7, New York
Entered as second-class matter at the Post Office at New York, N. Y.

DISCHARGED

The ultimate goal of every psychiatrist is to see his hospitalized patients discharged. Pacatal can help in attaining this objective. Pacatal is ideal for patients with a promising future—those who have been hospitalized less than two years—because it keeps them accessible, ambulatory, and alert. On Pacatal, patients display a greater warmth of personality and willingness to cooperate. They are more responsive to psychotherapy and are able to establish a better relationship within their environment.

In a one-year follow-up study of 67 schizophrenic patients treated with Pacatal, Vorbusch[1] found that 23 (or 34 per cent) were able to leave the hospital, and only 6 had to return for further treatment. A similar report by Feldman[2] noted a 36 per cent release rate in Pacatal-treated patients, with only 9 per cent returning from parole.

Dosage: Institutionalized patients—range 100 to 500 mg. per day (average 300 mg.). Usually begin with 50 mg. b.i.d., increase by 50 mg. every 5 to 7 days. *Ambulatory patients*—symptoms usually controlled with 25 mg. 3 or 4 times daily.

Supplied: 25 and 50 mg. tablets in bottles of 100 or 500. Available in 2 cc. ampuls (25 mg./cc.) for parenteral use.

References: 1. Vorbusch, H. J.: J. Clin. & Exper. Psychopath., (Jan.-Mar.) 1959
2. Feldman, P. E.: Am. J. Psychiat. *115*:736 (Feb.) 1959.

for normalization . . . not sedation

Pacatal®

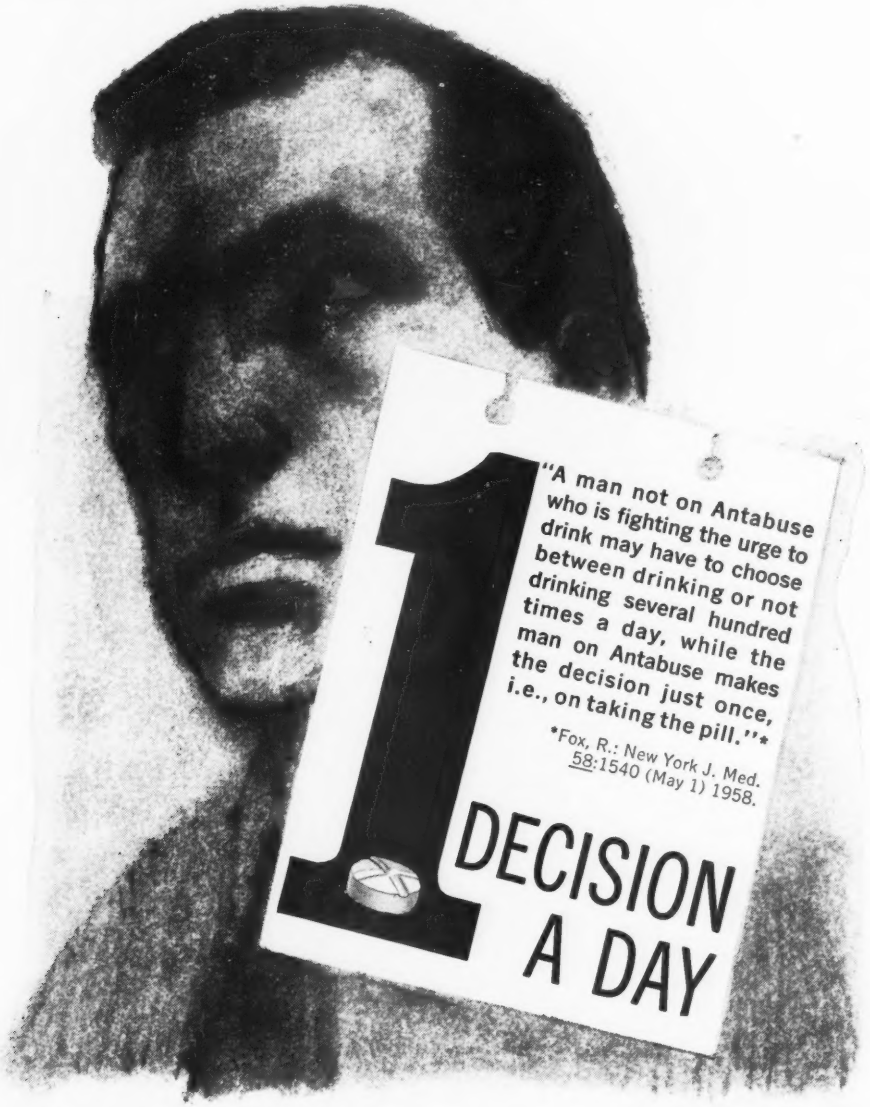
brand of mepazine

WARNER CHILCOTT

MORRIS PLAINS, N. J.

"ANTABUSE"® CLINICALLY PROVED IN ALCOHOLISM

a "chemical fence" for the alcoholic


"A man not on Antabuse who is fighting the urge to drink may have to choose between drinking or not drinking several hundred times a day, while the man on Antabuse makes the decision just once, i.e., on taking the pill."*
*Fox, R.: New York J. Med. 58:1540 (May 1) 1958.
1 DECISION A DAY

"ANTABUSE" helps the patient resist his compulsive craving for alcohol. With one dose a day he finds he cannot tolerate alcohol without experiencing extreme discomfort. By keeping the patient away from alcohol, "ANTABUSE" serves as a valuable adjunct to psychotherapeutic measures for the correction of underlying personality disorders.

"Antabuse," brand of DISULFIRAM (tetraethylthiuram disulfide), is supplied in 0.5 Gm. tablets (scored), bottles of 50 and 1,000. Complete information available on request.

Ayerst

AYERST LABORATORIES
New York 16, N.Y. • Montreal, Canada
5906

REITER MODEL SOS PROVIDES FOR ALL THE FOLLOWING TECHNIQUES:

CONVULSIVE THERAPY (maximum convulsive and therapeutic efficiency) • **NON-CONVULSIVE THERAPIES** • **ELECTRO-SLEEP THERAPY** • **FOCAL TREATMENT** (unilateral and bilateral) • **MONO-POLAR TREATMENT** (non-convulsive or convulsive) • **BARBITURATE COMA** (and other respiratory problems) • **MILD SEDAC** (without sedation) **DEEP SEDAC THERAPY** (with sedation) • **PRE-CONVULSIVE SEDAC** (for anxious patients who resist EST) • **POST-CONVULSIVE SEDAC** (for deep sleep) • **NEUROLOGICAL CONDITIONS** • **MEASUREMENT PROCEDURES**

faster therapeutic response with

REITER MODEL SOS

the one instrument combining the strongest convulsive currents with powerful yet gentle sedative currents

- exceptionally fast clinical therapeutic response
- most efficient convulsive currents result in minimal side effects—apnea, thrust, confusion and treatment-generated anxiety are negligible
- patients are quickly clear and bright following treatment
- difficult cases have responded to SedAc deep sleep therapy—powerful, deep, effective yet safe treatments are easily applied
- SedAc current establishes better transference — patients become communicative
- anxious aversion to EST minimized by gentle SedAc current
- one-knob, with safety lock, controls convulsive and sedative currents
- clinical studies have evaluated a new measurement procedure to determine areas of cerebral damage and the degree of malfunction

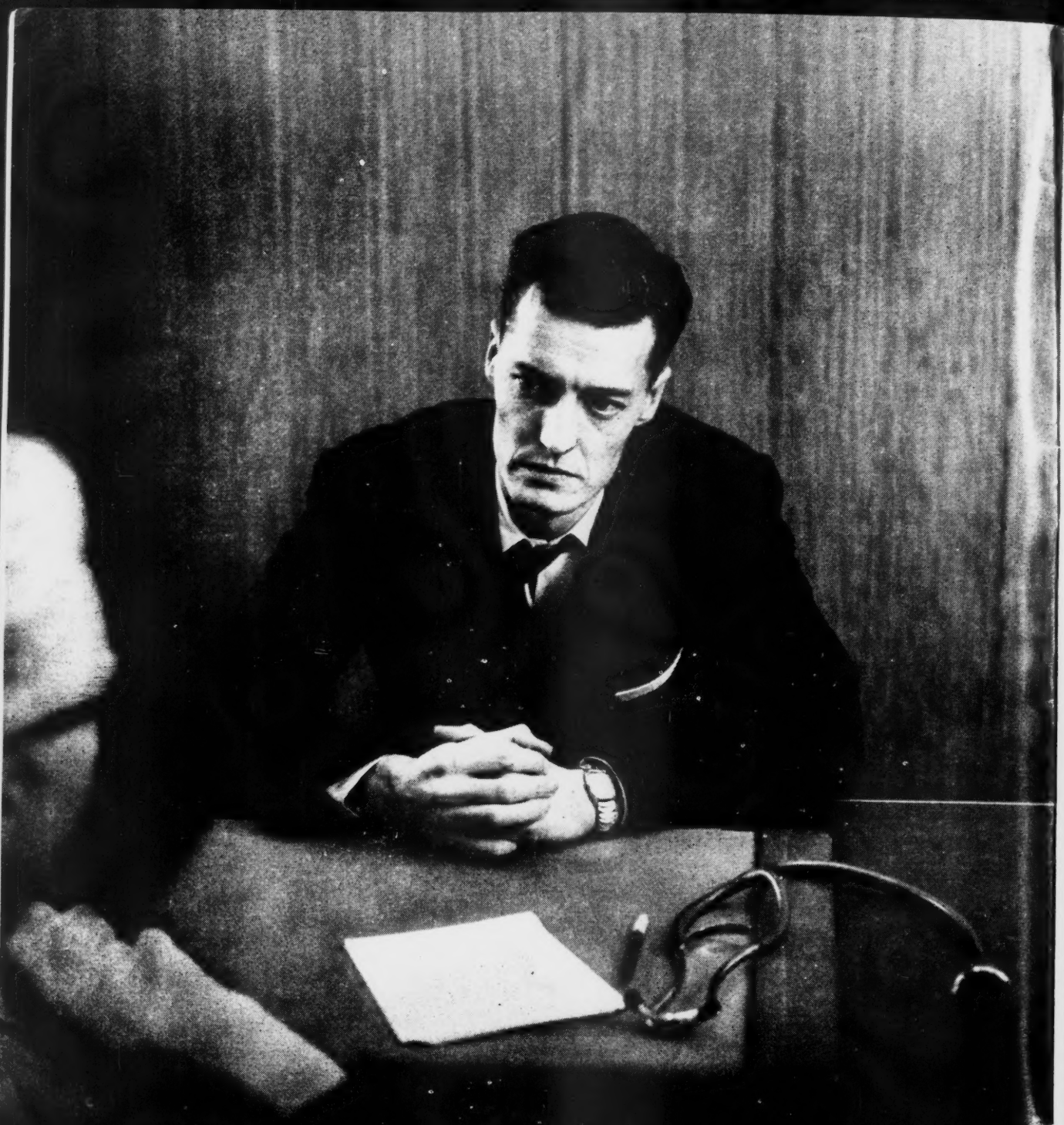
Model SOS contains the Reiter unidirectional currents and three SedAc ranges as part of the single selector control. Other models available are: 1. Model S containing only the unidirectional currents; 2. SedAc (attachment) to be used with Model S; 3. SedAc (self-powered) an independent instrument.

Only Reiter, the original unidirectional current electrostimulators, are authentically backed by extensive clinical experience with over 200 references in literature and text-books.

Literature and bibliography on request.

REUBEN REITER, Sc.D.

64 WEST 48th STREET, NEW YORK 36, N. Y.



HELPS YOU OBTAIN EARLY RESULTS IN DEPRESSION

- *Helps improve mood and outlook* . . . from the beginning of psychotherapy. Rapidly relieves crying spells, apprehension, rumination, insomnia.
- *Facilitates psychotherapy* . . . patients become more readily accessible and communicative. Improves possibility of recovery without electroshock.

▲Deprol▲†

MARKED IMPROVEMENT WITH ▲Deprol▲ REPORTED IN THREE PSYCHIATRIC STUDIES

	STUDY #1	STUDY #2	STUDY #3
NUMBER OF PATIENTS	135	35	52
TYPE OF PATIENTS	Depressed, chronic psychotic patients, mostly schizophrenic (hospitalized)	26 psychotic depressions, manic-depressive and involutional; 9 neurotic depressions (private practice).	36 involutional depressions, av. age 77 (custodial patients in nursing home); 16 reactive depressions, av. age 65 (private practice).
DOSAGE	1-4 tabs. q.i.d. (av. 2 tabs. q.i.d.)	1-3 tabs. q.i.d.	1-2 tabs. t.i.d. or q.i.d.
DURATION OF TREATMENT	1 wk.-17 mos., (av. 1.8 mos.)	1-25 wks. (av. 8 wks.)	6-22 wks.
RESULTS	Substantial improvement in 41%; some improvement in an additional 39%.[1]	Complete or social recovery in 57%.[2]	Good results in 78% of involutional depressions and in 69% of reactive depressions.[3]

ADVANTAGES OF ▲Deprol▲

- Antidepressant action does not produce excessive stimulation, jitters, insomnia
- Restores normal sleep without depression-producing aftereffects
- Improves mood without depressing appetite

DOCUMENTED SAFETY[1-4]

- Deprol has not produced hypotension or liver toxicity
- Does not interfere with other drug therapies, or with sexual function
- Can be used in hypertension, and with unstable personalities
- Side effects are minimal

Composition: Each light-pink, scored tablet contains 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate.

Dosage: Usual starting dose is 1 tablet q.i.d. When necessary, this dose may be gradually increased up to 3 tablets q.i.d.

References:
1. Pennington, V.M.: The use of Deprol in chronic psychotic patients. Am. J. Psychiat. 115:250, Sept. 1958. **2.** Alexander, L.: Chemotherapy of depression—Use of meprobamate combined with benactyzine (2-diethylaminoethyl benzilate) hydrochloride. J.A.M.A. 166:1019, March 1, 1958. **3.** Settel, E.: Treatment of depression in the elderly with a meprobamate-benactyzine hydrochloride combination. Submitted for publication, 1958. **4.** Personal communications from physicians; in the files of Wallace Laboratories.

WALLACE LABORATORIES
New Brunswick, N. J.

CD-8680

†TRADE-MARK

Volume XX MAY 1959 Number 5

DISEASES *of the* Nervous System

Contents

CUMULATIVE INDEX OF ANTIDEPRESSANT MEDICATIONS 197
Nathan Thal

ADMINISTRATION OF TARAXEIN IN HUMANS 206
Robert G. Heath, Sheldon B. Cohen, Francisco Silva, Byron E. Leach and Matthew Cohen

PROGNOSTIC VALUE OF THE MECHOLYL TEST 209
A. Hoffer and M. J. Callbeck

COLOR ANALYSIS OF THE PYRAMID TEST 211
P. O. O'Reilly and Duncan Blewett

SURVEY OF MODIFIED ELECTROSHOCK THERAPY 213
Oscar Rozett

EVALUATION OF DEPROL IN PSYCHIATRIC OUT-PATIENTS 216
Donald D. Lathrop

MULTIPLE SCLEROSIS AND RHEUMATIC FEVER: RELATED DISEASES 221
Dewey K. Ziegler

DRUG DELIRIUM DUE TO MEPROBAMATE 225
Harry F. Darling

BOOK REVIEWS 225

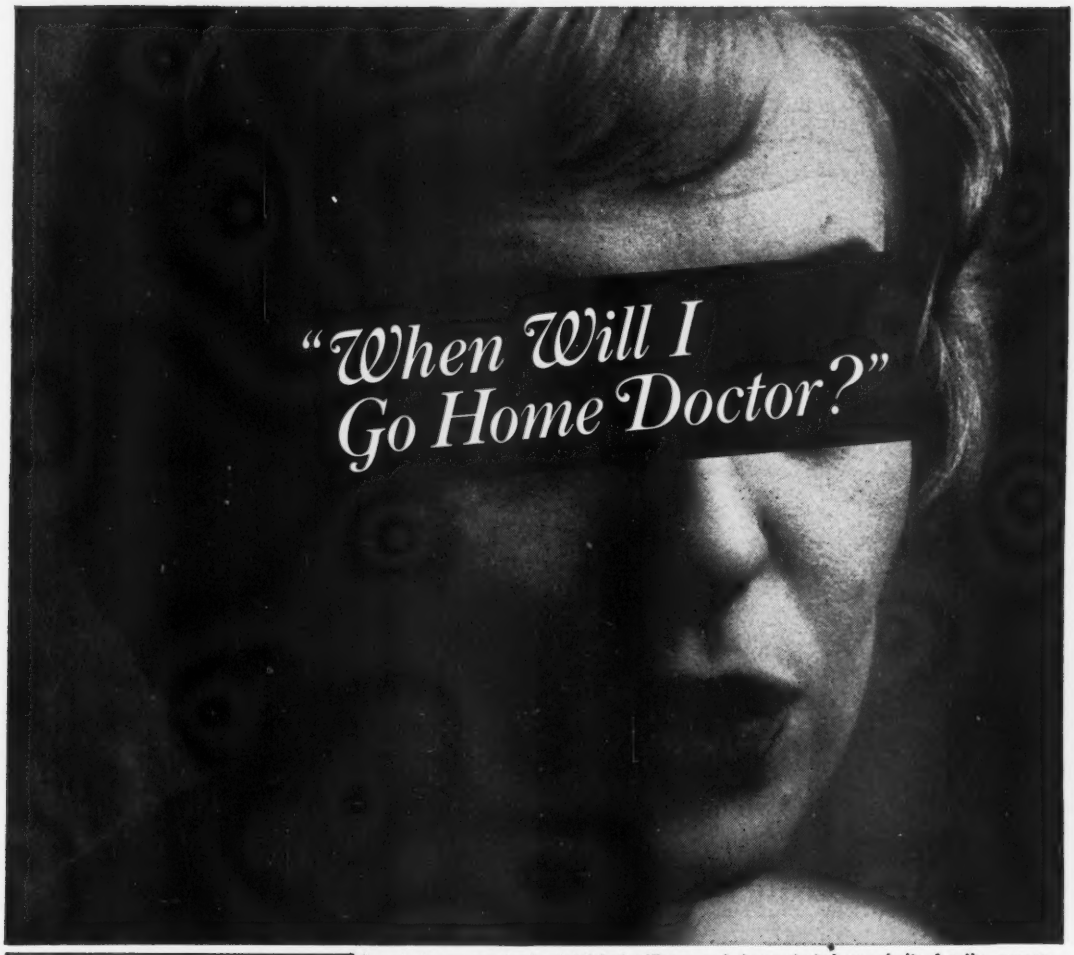
EDITOR
Titus H. Harris, M.D. 112 North Boulevard, Galveston, Texas

MANAGING EDITOR
George Bisgeir, B.S., LL.B. New York, New York

ASSOCIATE EDITORS

A. F. Bennett, M.D.----------Berkeley, California
Francis J. Braceland, M.D.-------Hartford, Conn.
Franklin G. Ebaugh, M.D.-------Denver, Colorado
Milton H. Erickson, M.D.--------Phoenix, Arizona
Hamilton Ford, M.D.-------------Galveston, Texas
Walter Freeman, M.D.-------Los Altos, California
A. Hauser, M.D.-------------------Houston, Texas
Louis J. Karnosh, M.D.----------Cleveland, Ohio
Frank H. Luton, M.D.-------Nashville, Tennessee
Wm. Malamud, M.D.-----------------Boston, Mass.
Karl A. Menninger, M.D.----------Topeka, Kansas
Hans H. Reese, M.D.---------Madison, Wisconsin
Lewis J. Siegal, M.D.-------New York, New York
Harry C. Solomon, M.D.-----------Boston, Mass.
S. Bernard Wortis, M.D.---------New York, N. Y.

YEARLY SUBSCRIPTION $6.00
Foreign Subscription $6.50



YOUR ANSWER MAY BE "I DON'T KNOW" OR "VERY SOON." VESPRIN MAY MAKE THE DIFFERENCE

Vesprin is an agent of established efficacy and demonstrated superiority for the management of psychotic patients. In schizophrenia, manic states, and psychoses associated with organic brain disease, Vesprin controls intractable behavior patterns making patients more accessible to psychotherapy. Excitement, panic, delusions, hostile behavior are moderated to permit early insight for rapid progress into resocialization and rehabilitation. **Not only is Vesprin your drug of choice for initial therapy, but it has proved effective in patients who failed to respond to other phenothiazines.**

Vesprin does not oversedate your patients into sleepiness, apathy or lethargy — and drug-induced agitation is minimal.[1] It is relatively free from side effects.[1,2] Skin eruptions, photosensitivity or hyperthermia have rarely been reported. Individual dosage levels are easily established. Intramuscular injection causes no pain or tissue irritation. Vesprin often brings improvement in chronically disturbed patients refractory to shock therapies and other drugs.[3,4]

VESPRIN

SQUIBB TRIFLUPROMAZINE HYDROCHLORIDE

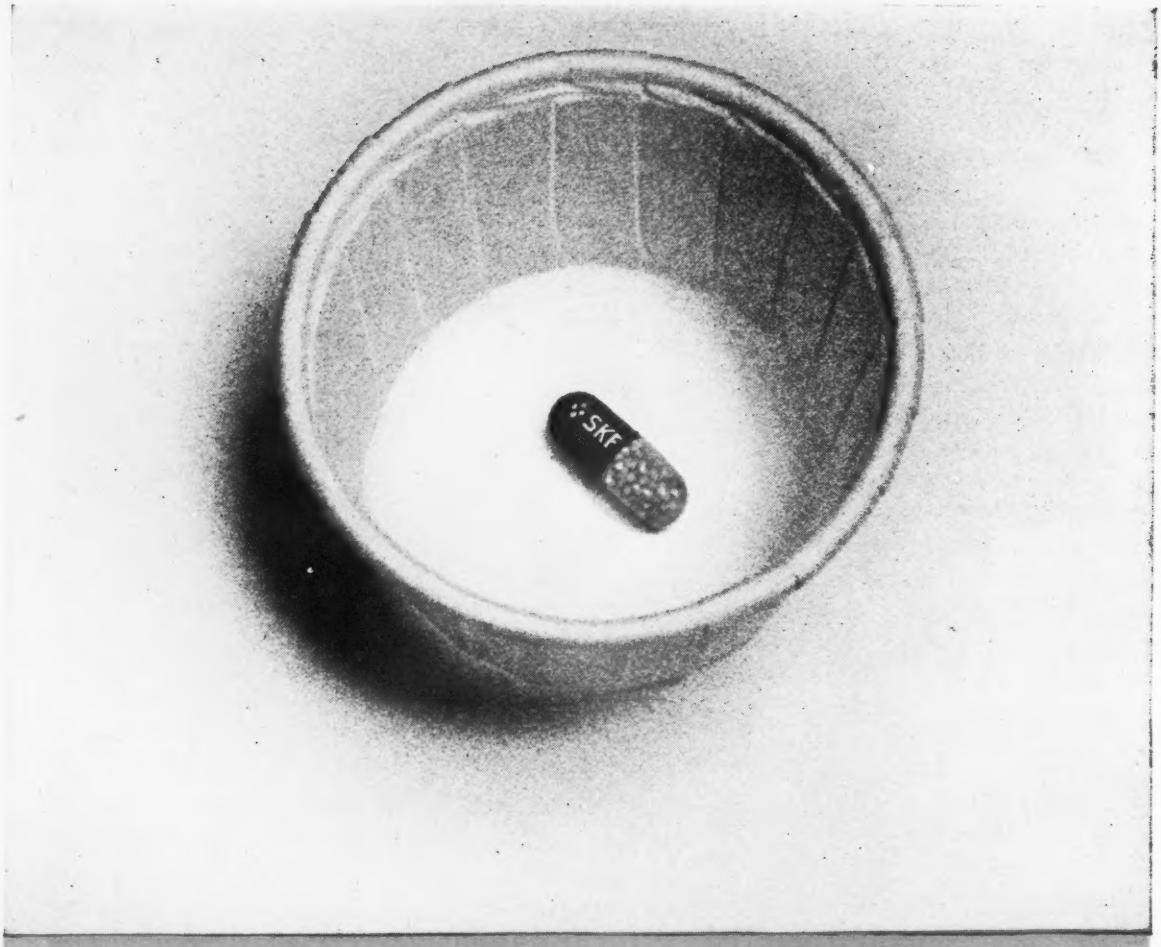
...a unique halogenated phenothiazine for the management of schizophrenia, manic states, psychoses associated with organic brain disease, senile psychoses, and primary behavior problems in children.

Dosage: Usual initial dose, 100 to 150 mg. daily, increased or decreased according to patient response. See literature. Supply: Tablets: 10, 25 and 50 mg., in bottles of 50 and 500. Capsules: 100 mg. in bottles of 50 and 500. Emulsion: 30 cc. dropper bottles and 120 cc. bottles (10 mg./cc.). Parenteral Solution: 1 cc. multiple dose vial (20 mg./cc.) and 10 cc. multiple dose vial (10 mg./cc.). Vesprin Injection Unimatic (15 mg. in 0.75 cc.).

SQUIBB Squibb Quality — the Priceless Ingredient

'VESPRIN'® AND 'UNIMATIC'® ARE SQUIBB TRADEMARKS

1. Goldman, D.: Am. J. M. Sc. 235:67 (Jan.) 1958. 2 Morehouse, W. G., and Freed, J. E.: Monographs on Therapy 3:32 (May) 1958. 3. Leger, Y.: Union Med. Canada 87:831 (July) 1958.
4. Bruckman, N. S.; Saunders, J. C., and Kline, N. S.: Monographs on Therapy 3:24 (May) 1958.



Better protection against relapse with Compazine* Spansule† capsules

With 'Compazine' Spansule capsule therapy you maintain firmer and more continuous control of psychotic behavior than with usual tablet therapy

Hard-won control of psychotic behavior is too often jeopardized by sudden falls in drug levels due to skipped or forgotten doses of t.i.d. and q.i.d. tablet medication.

Because one 'Spansule' capsule sustains an unvarying therapeutic level of 'Compazine' for 10 to 12 hours, 'Compazine' *Spansule* capsule therapy protects your patient from these sudden falls in drug levels that may lead to a breakthrough of symptoms.

Administered only q12h, 'Compazine' *Spansule* capsules help you maintain continuous, all-day and all-night control of psychotic behavior.

Available: NEW 75 mg. 'Compazine' *Spansule* capsules—also in strengths of 10 mg., 15 mg. and 30 mg.

If it's a 'Spansule' brand capsule, it's made and marketed only by

Smith Kline & French Laboratories

first ⧗ in sustained release oral medication

*T.M. Reg. U.S. Pat. Off. for prochlorperazine, S.K.F.
†T.M. Reg. U.S. Pat. Off. for sustained release capsules, S.K.F.

MEDICAL LIBRARY
HISTORICAL BUILDING
DES MOINES, IOWA

Volume XX MAY 1959 Number 5

DISEASES *of the* Nervous System

A PRACTICAL JOURNAL ON PSYCHIATRY AND NEUROLOGY

Cumulative Index of Antidepressant Medications

NATHAN THAL, M.D.

The fundamental purpose of medication is to supply the organism with chemical substances calculated to prevent or restore a shift in the state of equilibrium. Although the laws governing the equilibrium of inorganic and organic reactions are well understood, the laws governing the biochemical reactions of living organisms are imperfectly comprehended since studies of biochemical processes have been handicapped by the fact that these reactions are part of the life process and therefore cannot be interrupted during the life of the organism.

Experimental investigation of the biochemical reactions of the body constitutuents was dramatically accomplished by Schoenheimer,[1] through the utilization of isotopes of elements that occur in organic matter—carbon, oxygen, hydrogen and nitrogen—as tracer substances. With this technique, he was able to label and mark organic molecules and to follow their progress and development through the metabolic cycles of the living organism. The result of these classic experiments completely destroyed the concepts of Helmholtz in which the living organism was equated to a combustion engine, where the food represented the fuel and the internal organs and structures were compared to the working parts of the machine. These concepts were replaced by Schoenheimer's postulates that all constituents of living matter, whether functional or structural, i.e., fuel or engine, were in a constant and continuous state of fluctuation and that all of the components of the organism participated actively in the metabolic processes. The concepts of modern biochemistry were therefore revised and reformulated to conform to the fact that despite the structural appearance of cells, tissues and organs and the apparent constancy in the mass of these structures, that they are never really the same since they are rapidly and continuously changing their constituents and are themselves active participants in biochemical processes and metabolic cycles. This concept implies that the brain, the spinal cord and the peripheral nerves, as well as other structural elements of the body, are all thermodynamically unstable since they are delicately balanced and interrelated biochemically with the functional metabolites or so-called "fuel" of the organism. In the interpretation of the results of his experimentations, Schoenheimer further points out that upon the cessation of the oxidative processes, following death, the unstable structural elements also collapse and that life continues only as long as the biochemical reactions of the organism remain balanced to maintain the structure of the organism and its component parts against its tendency to lose its identity and configuration.

In the domain of atomic and molecular physics, the dynamic concepts of the structure of matter have long been accepted. The teachings that molecular bombardment and reactions are constantly taking place in seemingly solid substances like metals and minerals are generally easily comprehended and seldom disputed. In the realm of the universe and space, the concepts that planetary systems are also unstable and exist only because they are retained in balance, rotation and interraction, have also become a part of our understanding of the nature of our world. In our social, economic and political structures, it has become increasingly apparent that these respective structures cannot exist independently and that the maintenance of their stability is totally dependent on the functional interractions of these structures in the total environment. The so-called "breakdowns" in atomic and

molecular structure, in biochemical and metabolic processes, in social, economic and political patterns or cultures and in universal bodies and planetary systems are therefore merely a manifestation of failure to maintain a potentially unstable internal structure in balance with an equally unstable external structure against its innate tendency to collapse. This same concept is equally applicable to interpersonal relationships. Interdependency therefore appears to be the key to the functions of all bodies.

The academic disciplines of biology, bacteriology and parasitology delineate the symbiotic relationships or balance between organisms both of the same and of different species. In animal and human physiology we learn of the equilibrium maintained between the living organism and the atmosphere as illustrated by the mechanics of respiration, temperature regulation, the partial pressures of atmospheric gases and the absorption, utilization and excretion of metabolic substances. In the domain of psychiatry, on the other hand, we often fail to grasp the concept of the interrelationship of mental processes in the metabolism between the organism and the social structure. In this respect, mental illness can be conceived as a failure of an individual organism to maintain its balance in the orbit of the social system.

In order for an unstable organism to maintain its structure as well as its position in the orbit of an equally unstable social system, energy is required. In the living organism these energy debts are paid by biochemical reactions. From an impersonal point of view, the incidence of mental illness is therefore a gauge of measurement of tilt or of the degree and direction of the imbalance in the social structure. Every imbalance or shift in equilibrium of the social system requires an additional expenditure of energy. To the extent or degree that the social structure remains unbalanced, its instability increases and its vulnerability to collapse becomes more apparent. Therefore, as more organisms in the social system become incapacitated in the direction of mental illness, the energy debts of the remaining organisms required to maintain the structure become greater. Eventually, more and more organisms become incapacitated as a result of the increased energy requirements assessed to each organism to maintain the balance of the system and the rapid acceleration of this vicious process results very quickly in a collapse and disintegration of the social structure.

In the successful maintenance of a social system, it therefore becomes imperative that efforts must constantly be made and energy expended to correct imbalances in individual organisms with utmost haste as well as to prevent any tendencies for individual or groups of organisms to succumb to psychiatric disorders. The utilization of psychiatric medications for this purpose is therefore never to be deplored.

From a philosophical point of view, the phrase, "survival of the fittest" has frequently been misrepresented by substituting the term "strongest" for the term "fittest," for it is certainly not the strongest organisms that have survived but the fittest or most adaptable, i.e., those organisms which have been able to remain in balance and equilibrium with other organisms and with their environment or habitat. Similarly, history is replete with social cultures and structures which have collapsed, not as a result of their lack of strength, but as a result of their inability to remain in equilibrium with other social structures. It is a common precept, in host-parasite relationships, that the destruction or collapse of one results in the demise of the other.

An attempt has been made to present the concept that both mental health and illness are not static but dynamic processes, the constituents of which are never the same from one moment to another. Mental processes are interrelated with the functional and structural constituents of ,the body, which are also in a constant state of flux, and are maintained in balance in a dynamic social system, which itself is constantly and rapidly changing.

In the treatment of mental disorder, the reversal of states of either excitation or depression has been of cardinal importance in psychiatric technique procedures. Prior to the development of ataraxic medications or tranquilizers, narcotics, sedatives, stimulants

and analeptics were utilized for this purpose. Recently many new biologic and synthetic preparations have become available and in the past several years the domain of ataraxic medications has expanded so enormously that the selection of individual drugs and varying drug combinations approaches infinity. However, as Alexander[2] has pointed out, these new drugs are best adapted to the treatment of states of excitation, with panic and anxiety, and especially mania. The drugs currently in vogue for the reversal of pathologic states of excitation have been primarily the phenothiazine derivatives, and to a lesser extent, the rauwolfia alkaloids and mephenesin or propanediol derivatives.

In contrast to the success attained in the treatment of states of excitation,[3] the reversal of pathologic states of depression through the utilization of central nervous system drugs has been far less gratifying. It has therefore been difficult in many instances to entirely abandon the use of electroshock therapy for severe depressive reactions. In an attempt to counteract depression, the effectiveness of a number of antidepressant agents have been subjected to clinical evaluation and study. Varying combinations of drugs have also been used in an effort to explore the possibilities of synergistic activity. As a result of these studies, the comparative efficacy of various preparations was evaluated and the more commonly encountered side effects and disadvantages were outlined. For comparative purposes, a series of untreated patients and a series of patients treated with electroconvulsive therapy were included in this study. An attempt was made to correlate various psychiatric entities and syndromes with their physiologic and neurologic concomitants in order to select medications for the treatment of these conditions which best meet the physiologic requisites of therapy. It is recognized that medications per se are not the ultimate solution in many psychiatric conditions, and where these conditions are apparent, the initially gratifying results of chemotherapy may be undermined unless further therapeutic efforts and rehabilitative measures are instituted and maintained.[4]

In the treatment of mental disorders, it may be categorically stated that patients experiencing syndromes associated with either severe excitation or depression of the nervous system must be hospitalized for therapy. Failure to accomplish hospitalization is probably the most frequent factor in unwittingly feeding and fostering continuation of the disease process through the mechanism of reinforcement. In this regard, chronic mental illness may be simply defined as neglected acute mental illness. Furthermore, patients who are subconsciously aware of their need for hospitalization cannot reconcile the seriousness of their illness with attempts to minimize their symptoms or to pacify or appease their needs.

Aside from promoting, encouraging, and fostering the illness, failure to accomplish hospitalization when the need is apparent has numerous inherent risks and hazards of a more urgent nature. In the case of depression, the greatest risk is that of suicide, while in the case of manic or catatonic excitement, the hazard of physical exhaustion, dehydration and acidosis is similarly tantamount to self destruction and may also be considered as suicidal. Since mentally ill persons are extremely sensitive to subconscious motives and intentions in others, any efforts to delay or discourage hospitalization during an episode or phase of acute excitation or suppression of cerebral function may readily be misinterpreted by the patient as evidence to support their suspicions of the therapist's motives.

Among the numerous advantages accruing to the patient, hospitalization affords an armamentarium of clinical and laboratory facilities and equipment for diagnosis and therapy generally unavailable to the solitary practitioner. The utilization and availability of intricate and expensive electronic devices, radiologic equipment, biochemical procedures, ultramicroscopic techniques and psychological studies comprise a few of the research and investigative tools of a contemporary psychiatric hospital. The multi-disciplinary approach to the disorders of psychogenic origin involves the combined efforts of experts in many fields of academic and clinical endeavor. Hospitalization therefore provides the patient maximum opportunity for recovery from psychiatric illness.

The selection of a drug or combination of

drugs for the treatment of disorders of psychogenic origin must be calculated to produce a predictable effect upon the central nervous system for it is through the action of drugs on the brain that functional alterations in psychic phenomena take place. Drugs exerting an effect on cerebral function may be classified according to their ability to alter the activity of the central nervous system. One of the most valuable contributions in the domain of psychiatry has been the development of pharmacologic agents capable of inducing artificial excitation or suppression of the central nervous system. The principal advantages of this group of drugs is the ability to produce a reversal or counteraction of increased or decreased cortical activity and to effect a restoration of normal brain function. This is accomplished by selective inhibition of aberrant subcortical activity without concurrently affecting cortical or medullary functions or impairing consciousness.

In the adaption of a particular drug to a specific psychiatric condition, it is necessary to ascertain the desirability of artificially producing a temporary state of excitation or depression, of altering functional reactions to stress, or of reversing psychiatric processes or patterns. Pharmacologic agents are generally employed to produce transient states of emergency energy to meet special needs or transient states of rest, lethargy or semiconsciousness in order to allow restorative processes to take place under the most optimal conditions. The advent of ataraxic drugs and psychic energizers, characterized by their ability to produce restoration of normal function without impairing sensory or motor activity, has permitted their use as therapeutic agents in psychiatry for the purpose of producing and maintaining the reversal of pathologic states of excitation or depression of psychiatric origin.

Method

Following a preliminary drug screening procedure, twenty groups of nine patients each were selected for treatment. Each group was composed entirely of severely depressed patients with a history of recent suicidal attempts either during their hospitalization or immediately preceding their admission. The ages of the patients in each group were about equally distributed in the range between 22 and 65 years. Both voluntary admissions and committed patients were included in each group. The patients in this series were selected to include all types of depression and represented the most acutely depressed patients with accompanying marked anorexia, weight loss, insomnia, feelings of unworthiness and suicidal ideation. The patients were further selected to include as much variability as possible with respect to duration of illness, total hospitalization, previous admissions and therapies. Since a parallel study could not be conducted because of the total number of patients involved, the studies were conducted in series with each group being treated and evaluated consecutively. The total number of patients included in this study over a period of ten months was 180.

For the purpose of evaluating the effectiveness of this new antidepressant agent, two groups of nine patients each were used as controls. The first group received no treatment other than the usual doctor-patient relationship, with no formal attempt at psychotherapy. Each patient was interviewed regularly in order to evaluate his progress and discuss his feelings and problems of hospitalization and therapy. In this group of untreated patients, two patients recovered spontaneously and were discharged from the hospital. The second group in this series was treated with electric shock therapy, utilizing a technique previously reported and employing as premedication meprobamate, 400 mgm. and atropine, grains 1/150 administered orally one hour prior to treatment.[5] In this group of patients treated with electroconvulsive therapy, eight patients recovered following four to eight treatments administered three times per week. No other treatment was employed in this group either during or following their series of electric shock treatments, other than the usual doctor-patient relationship mentioned previously.

Prior to release from the hospital, each patient in this consecutive series of studies was presented to and interviewed by the full medical staff of the hospital, comprising about 20 physicians and psychiatrists. The

interview was preceded by a complete case presentation by the attending physician or psychiatrist and was followed by a staff vote and decision as to whether the patient had made a psychiatric and social recovery. In accordance with hospital custom, terminal leaves and discharges were authorized and granted by the full medical and psychiatric staff.

Prior to the initiation of this study, 11 individual preparations and two drug combinations were subjected to clinical evaluation. All the medications were administered orally in tablet form. The dosages prescribed varied with each preparation and optimal rather than maximal dosages were used. The optimal dose was determined on the basis of empirical evaluation from previous studies. Where previous studies were inadequate or unavailable, the average dose recommended by the pharmaceutical manufacturer was employed. All drugs were administered two times to three times daily in equal or divided dosage. Drugs which had not been thoroughly screened previously were subjected to comprehensive hematologic and blood chemistry studies weekly with simultaneous recordings of weights and blood pressures. The duration of treatment with each drug was arbitrarily limited to 30 days and then abruptly discontinued. The patients were subsequently followed for a varying period of time depending upon the progress and response to treatment.

It is recognized that a group of nine patients does not constitute a statistically valid study. However, it was felt that smaller groups were preferred for this particular comparative evaluation since this was essentially a screening procedure and because a thorough, comprehensive and accurate clinical evaluation of the responses of each patient on a daily basis could not be accomplished by a single examiner with more than nine patients treated and studied at one time. The drugs and drug combinations used in this prior screening process and the results of this comparative evaluation are tabulated in Table I. In evaluating the "effectiveness" of each agent or group of agents, the onset, duration and nature of the responses in each individual patient were given equal priority with the total number of patients recovered and discharged in each particular group.

Results

The results of the initial screening procedure yielded considerable information regarding the effectiveness of certain groups of drugs in the treatment of depression.

In general, the amphetamines were considered totally ineffectual. This group of drugs is characterized by an initial stimulating effect, cortical depression and fatigue ensues. The end result is an aggravation of the depression. The amphetamines are therefore contraindicated in depression although they remain useful as antidotes in counteracting toxic effects or overdosage of various cortical depressants or poisons. Their employment should be confined to medical emergencies rather than to the treatment of psychiatric disorders.

Ritalin® may be used in treatment of mild exogenous depression but the results obtained from this study do not justify its use as an antidepressant agent in either neurotic or psychotic depressions. It remains useful in the treatment of post-alcoholic depression in combination with thiamine. It also retains its usefulness in counteracting the lethargy and dullness produced by anticonvulsants in the treatment of epilepsy and in elderly patients for improving senile psychomotor activity and behavior. As with the amphetamines, it is also a useful antidote to overdosages of barbiturates or ataraxics.

The nicotinic acid derivatives are all about 40-50 per cent effective in the treatment of depression. This effectiveness is probably attributable to their role in the biochemical oxidative processes of brain cell metabolism rather than to vasodilatation and increased effective antidepressant and does not produce increased intracranial blood flow. They are therefore preferred to nicotinic acid because of the absence of side effects due to vasodilatation.

Benactyzine and mepazine are both ineffectual antidepressants. The former drug is characterized by its anticholinergic properties and the almost entire absence of other physiologic effects. The latter drug produces a mild stimulating effect on psychomotor activity, behavior and mood. It also has some synergistic activity with chlor-

TABLE I—*Effectiveness of Antidepressant Medications*

Drug or Agent	Dosage Schedule	Duration	Disadvantages	Side Effects	Series	Recovered	Discharged	Effectiveness
Benzene Nucleus			AMPHETAMINES					
Amphetamine (Benzedrine)	5 mgm t.i.d.	30 days	Habit formation Circulatory Collapse Weight loss	Nervousness Irritability Insomnia Hypertension	9	2	2	Poor
D-amphetamine (Dexedrine)	5 mgm t.i.d.	30 days	Habit formation Weight loss Fatigue	Nervousness Insomnia Anorexia	9	2	2	Poor
Methamphetamine (Methedrine)	2.5 mgm t.i.d.	30 days	Arrrhythmias Hallucinations Slow metabolism Slow excretion	Nervousness Twitching Insomnia Anorexia	9	2	2	Poor
Benzene & Pyridine Nuclei			PHENIDYL DERIVATIVES					
Methylphenidyl Acetate (Ritalin)	10 mgm t.i.d.	30 days	None	Nervousness Insomnia Anorexia Dizziness Nausea Headache	9	3	3	Fair
Pyridine Nucleus			NICOTINIC ACID DERIVATIVES					
Nicotinic Acid (Niacin)	100 mgm t.i.d.	30 days	None	Flushing Itching Burning Dizziness Vomiting Headache	9	4	4	Fair
Nicotinamide	100 mgm t.i.d.	30 days	None	Headache Nausea Dizziness	9	4	4	Fair
Isonicotinyl-Hydrazine (Isoniazid)	100 mgm t.i.d.	30 days	None	Nausea Vomiting Dizziness Headache	9	4	4	Fair
Iproniazid (Marsilid)	25 mgm t.i.d.	30 days	None	Hypotension Dryness Edema Delayed Micturition Impotence	9	5	5	Good
Dibenzene Nucleus			DIPHENYL DERIVATIVES					
Benactyzine (Suavitil)	1 mgm t.i.d.	30 days	None	Nausea Dizziness Dryness Blurring	9	3	3	Fair
			DRUG COMBINATIONS					
Benactyzine Meprobamate (Deprol)	1 mgm t.i.d. 400 mgm t.i.d.	30 days	None	Nausea Dizziness Dryness Blurring	9	4	4	Fair
Iproniazid Mepazine Nicotinic Acid Thiamine HCL	25 mgm) 50 mgm) 50 mgm) t.i.d. 25 mgm)	30 days	None	Hypotension Weakness Dizziness Nausea Impotence	9	5	5	Good
Phenothiazine Nucleus			ATARAXIC DRUGS					
Mepazine (Pacatal)	50 mgm t.i.d	30 days	None	Drowsiness	9	4	4	Fair
Benzene Nucleus			PHENYLETHYL DERIVATIVES					
B-phenylethyl-hydrazine (W-1544A) (Nardil)	25 mgm t.i.d.	30 days	None	Hypotension Dizziness	9	7	7	Excellent

promazine and is useful in counteracting drug depressions as well as in post-alcoholic depressions.

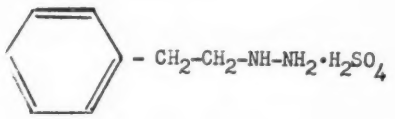
Because of the excellent responses obtained with Nardil,® this series was expanded from 9 to 180 patients. The results of this expanded study essentially confirmed the impressions derived from the initial screening procedure; 144 patients recovered and were released from the hospital following 30 to 60 days of therapy. The remaining 36 patients required supplementary medications which included phenothiazines and meprobamate. In general, those patients who failed to respond to therapy had complicating conditions, such as an underlying schizophrenic process, deep-seated psychoneurotic disorder or chronic brain syndrome, thereby requiring more extensive and prolonged therapy. However, no patient in this study made insufficient improvement on chemotherapy to necessitate the utilization of electroshock treatment.

Side effects of Nardil occurred very rarely and consisted of transient orthostatic hypotension associated with weakness and dizziness. The drug was discontinued only on two patients as a result of the discomfort they experienced due to a drop in systolic pressure to 80 and 75 mm of Hg. respectively. However, the hypotension generally did not occur until three or four weeks following the onset of therapy when considerable improvement or recovery from the depression had already been accomplished. Both of these patients continued to show progressive improvement after cessation of the drug and were discharged as recovered two and three weeks after discontinuation of therapy.

Weekly laboratory studies were performed on all patients and no abnormalities were encountered. These studies included a complete blood count, liver function tests, renal function tests, blood sugar and other blood chemistry examinations as indicated. T.P.R.'s and blood pressures were taken bi-weekly or more frequently if abnormalities were encountered. Except for occasional upper respiratory infections or mild gastrointestinal disturbances, no intercurrent illnesses were encountered which required a discontinuation or reduction in medication.

Nardil®

B-Phenylethylhydrazine (W-1544A) is a sympathomimetic amine and a potent inhibitor of amino oxydase activity. The monoamine oxydase inhibition is of rapid onset and prolonged duration. The drug is administered orally as the sulfate salt, which upon reaching the stomach is converted to the hydrochloride. It is completely absorbed from the gastrointestinal tract. Occasional side effects reported consist of nervousness, drowsiness, headache, nausea and hypotension. No toxic effects on the blood, kidneys or liver have been encountered. B-Phenylethylhydrazine may have a cumulative action on prolonged administration. It is a white, water soluble powder and has the following structural formula:



In the treatment of depression, B-Phenylethylhydrazine is an excellent antidepressant agent. The onset of antidepressant activity is very rapid and patients experience a "boost" or "lift" in mood within four to eight hours following commencement of therapy. This elevation in mood is accompanied by an increase in energy and a subjective feeling of "wanting to do things." This increase in energy generally persists throughout the period of therapy. Most patients express that they feel like they are taking a "high-powered vitamin"; that they want to keep active; that they feel more alert and energetic and that they experience no sense of nervousness or untoward effects from the drug. Suicidal ideation, ruminative thinking and self-depreciatory feelings subside very rapidly. Sleep is markedly improved qualitatively but not quantitatively. Patients expressed that they sleep more soundly and feel more rested upon awakening but do not sleep longer than their customary number of hours. They state that they feel like they've really had a good night's sleep and feel as though they have really slept soundly and undisturbed. Improvement is progressive and recovery from depression generally occurs within two to

three weeks. Appetite is improved and patients experience a sensation of relaxation despite an increase in psychomotor activity. Incidental effects noted during the study include a decrease in the desire or need for smoking and most patients stated that they do not experience a craving for cigarettes. Patients who were accustomed to smoking 40 or more cigarettes per day voluntarily reduced their consumption of tobacco to 10 cigarettes per day. Some patients remarked that they could do without cigarettes altogether. Following cessation of therapy, depressive symptoms did not recur and recovery was maintained. One case of transient impotence was encountered. The patient stated that he still maintained the desire for intercourse but had difficulty in maintaining an erection. This progressively improved following discontinuation of therapy and subsided in about two weeks following treatment.

In general, B-Phenylethylhydrazine is most useful in pure and uncomplicated depressions of the psychotic, involutional and psychoneurotic variety. In schizophrenic reactions with depressive features and in depressions associated with delusions, hallucinations and marked somatic symptomology or conversion reactions, the drug is less effective in the dosage prescribed. The drug has marked antihypertensive properties and patients with elevated blood pressures of functional origin responded very favorably.

Progressive weight gain was encountered in almost all patients during the course of treatment. This increase in weight was more prominent in patients who were initially underweight than in patients who were of average weight. Patients who had lost a great deal of weight prior to hospitalization as a result or concomitant of their depressive illness regained their normal weight within thirty days following commencement of therapy.

In the group of nine patients initially treated and studied in the screening procedure, seven patients recovered from their respective depressive illnesses. Three patients recovered and were discharged from the hospital following two weeks of therapy; the remainder recovered within thirty to sixty days. The two patients who remained unrecovered were improved from their depression but retained their psychosomatic symptomology and psychoneurotic features despite the alleviation of the associated depression. No patient in this series or in the expanded study made any suicidal attempt during or following the course of treatment or expressed any suicidal or self-depreciatory ideation. This drug was therefore considered to be the most valuable anti-depressant agent in this study.

Discussion

The substitution of drugs for electroshock therapy in the treatment of depressions remains experimental, since the reversal of depressive states with electroconvulsive therapy can almost be guaranteed, with or without any attempt at psychotherapy. Kalinowsky[6] states unequivocally that electric shock therapy is indicated in all types of depressions; that the treatment of depressions with convulsive therapy is the most widely recognized achievement in the field of organic treatment in psychiatry; that the response of depressions to usually less than five convulsions is one of the most predictable events in psychiatric treatment; that a uniformly high remission rate can be obtained without any psychotherapeutic effort other than the usual patient-doctor relationship; that cases followed by combined and intensive, competent psychotherapy fail to show a higher remission rate than those treated with electroshock alone, and that the superiority of electric shock treatment over psychotherapy in depressions cannot be disputed in the light of overwhelming clinical experience. So far, no chemotherapeutic agent or even combination of such agents has survived to meet this challenge. The enviable record established for the electroconvulsive treatment of depression will indeed prove difficult to surpass.

It is indeed unfortunate that the overwhelming therapeutic success of electroconvulsive therapy in depression has only been rivaled by the equally fruitless and sterile opportunities afforded by this therapeutic technique for experimentation into the etiology of depression or the mechanism of action responsible for the therapeutic suc-

cess of this procedure. The mechanism by which states of depression are alleviated by electric shock treatment remains as elusive today as the day it was empirically established as an effective therapeutic measure. The only available clue is that it is somehow the convulsion, whether induced spontaneously, pharmacologically or electrically, that is responsible for the therapeutic alleviation of depressive reactions. In the absence of opportunities for etiologic experimentation in electric shock therapy as well as the concomitant circumstances of unavailable effective antidepressant agents, much of the clinical research in depression has been confined to modification of treatment techniques and premedication for electroshock therapy.[5] The etiologic theories of depression have originated primarily from studies of the biochemistry of brain tissue. Mann and Quastel[7] demonstrated that aldehydes, resulting from the action of amine oxidase enzymes on a variety of amines, inhibit brain respiration by causing a reduction in the rate of oxygen absorption by brain tissue. They further demonstrated that benzedrine, an effective antidepressant, acts by blocking the amine oxydases. This inhibits the formation of aldehydes thus preventing the reduction in the rate of oxygen absorption. The blocking of the amine oxydase by benzedrine is accomplished by competing with the amines for these enzymes. This competition of benzedrine with the amines follows the laws of mass action.

Sperry[8] speculates that if benzedrine acts on a depressed patient by blocking the amine oxidases, the cause—or at least one of the causes—of depression is the (pathologic) formation of aldehydes by the oxidative deamination of amines. Recently, this theory has been further substantiated by the development of a new drug, iproniazid (Marsilid®), which in a manner similar to benzedrine, acts by inhibiting or competing for the amine oxydases. Iproniazid is a more potent amine oxydase inhibitor than benzedrine and simultaneously a more potent and effective antidepressant. Unfortunately however, iproniazid may have some very undesirable side effect on the liver and bone marrow with excessive and prolonged therapy.

It has been shown that there is a wide variety of compounds which inhibit the amine oxydase enzymes. The inhibition of some drugs is reversible while the inhibition of other compounds is not. The degree of inhibition as well as the effectiveness varies markedly with each preparation. While some drugs are very potent inhibitors, others are relatively feeble; while some are rapid acting, others are slow acting and while some are long lasting, others have inhibiting properties of short duration. Further, some are monoamine oxydase inhibitors while others are diamine oxydase inhibitors and still others may inhibit both to varying degrees. It is therefore quite apparent that amine oxydase inhibition is a complex phenomenon. Among the compounds that exhibit varying degrees of inhibition of the enzyme monoamine oxydase are many derivatives of phenylisopropylamine, amidines, methelene-blue, sulfhydril reagents, octyl alcohol, local anesthetics, antihistamines, sympathetic blocking agents, xanthine derivatives and other individual preparations.

If it is true that depressive reactions are the result of the formation of aldehydes in brain tissue as a consequence of the oxidative deaminization of amines by amine oxydase enzymes and that the blocking or destruction of these enzymes produces a therapeutic effect on the depression, then we may speculate further on (1) the mechanism by which spontaneous recovery eventually takes place and (2) the mechanism of action by which electroshock expedites this process. Assuming that enzymes are vulnerable to destruction by anoxia, the spontaneous recoveries or remissions may be accounted for by the hypothesis that as the aldehydes inhibit the uptake of oxygen by the brain, the resulting anoxemia destroys the amine oxydases thus preventing the formation of further aldehydes and eventually reversing the biochemical process. Electroshock may therefore act as a catalytic agent on the recovery process by accentuating the inhibition of brain tissue respiration produced by the aldehydes. The anoxia accompanying and following the electrically induced convulsion, by selectively destroying the amine oxydase enzymes, may be the mechanism of action by which electroshock expedites re-

covery from depression. In this respect, it is interesting to note that periods of artificially induced anoxia must be spaced over a period of two to three weeks for optimal therapeutic results and that more frequent or intensive therapy does not further shorten the recovery process.

Summary and Conclusions

A preliminary screening procedure was conducted over a period of 15 months in order to evaluate the effectiveness of a number of antidepressant medications. Eleven individual preparations and two drug combinations were studied. Two groups of nine patients were used as controls—the first group received no treatment and the second group was treated with electroconvulsive therapy. As a result of this investigation, B-Phenylethylhydrazine was selected as the most promising chemotherapeutic agent in depression.

A total of 180 patients with depressions of both endogenous and exogenous origin was treated with this drug for varying periods ranging from 30 to 60 days. This study was conducted over a period of 10 months and comprised twenty series of nine patients.

In the treatment of depression, the response to this antidepressant therapy approaches the response generally obtained from electroshock therapy; 80 per cent of patients were discharged from the hospital as recovered within 60 to 90 days following commencement of treatment with Nardil.® The remaining 20 per cent improved with supplementary medications to the extent that electroshock treatment was never required. No significant side effects on laboratory abnormalities were encountered.

BIBLIOGRAPHY

1. Schoenheimer, R.: The Dynamic State of Body Constituents. *Harvard University Press*, 1942.
2. Alexander, L.: Chemotherapy of Depression. *J.A.M.A.*, 166:9, Mar. 1, 1958.
3. Thal, N.: Clinical Evaluation of Chlorpromazine Therapy for Psychiatric Disorders. *Northwest Medicine*, 55:653-6, June 1956.
4. Thal, N.: Maintenance Therapy for Mental Patients. *Postgraduate Medicine*, 24:6, December, 1958.
5. Thal, N.: Premedication for Electroshock Treatment. *Dis. Nerv. System*, 17:2, Feb. 1956.
6. Kalinowsky, L.: Electroconvulsive Therapy of Depressions. Chap. 12, *Hoch and Zubin.*
7. Mann, P. J. G., and Quastel, J. H.: Benzedrine and Brain Metabolism. *Biochem. J.*, 34:414, 1940.
8. Sperry, M.: The Biochemistry of Depressions. Chap. 6, Hoch and Zubin. Depression. *Grune & Stratton*, New York 1954. P. 83.

Administration of Taraxein in Humans

ROBERT G. HEATH, M.D., SHELDON B. COHEN, M.D., FRANCISCO SILVA, M.D., BYRON E. LEACH, PH.D., and MATTHEW COHEN

In 1956[1] Heath and co-workers reported the isolation of a large protein molecule fractioned from the serum of schizophrenic patients. This substance was called taraxein because upon intravenous injection into human volunteers it produced symptoms which were thought to be characteristic of schizophrenia. This paper is designed to collect and summarize the highlights of clinical data relating to the effect of taraxein in humans.

Since this original isolation of taraxein at Tulane, two other laboratories have reported successful isolation of the substance and administration to volunteers with production of psychotic symptoms. Another laboratory was unsuccessful in isolating this fraction.

The technique employed in administration is to rapidly inject intravenously one to three ml. of taraxein, the amount derived from 400 ml. of schizophrenic serum. The symptoms, which we feel to be characteristic of schizophrenia, begin gradually, between two to 10 minutes after injection, increase slowly in intensity and reach a peak in 15 to 40 minutes. After this time they gradually subside, disappearing completely within two hours. One exception was a psychotic patient in whom the injection of taraxein during remission produced a prompt exacerba-

From Dept. of Psychiatry and Neurology, Tulane University School of Medicine.

Read at the annual meeting of Southern Psychiatric Association, Nashville, Tennessee, October 1958.

tion of symptoms. Behavioral changes produced by taraxein are different from those found upon the administration of LSD. D-LSD-25 has been given to a number of medical students, producing the usual psychotic phenomena, but in processing their blood before and at the peak of the LSD reaction, we could obtain no taraxein.

To date active taraxein has been given to 23 human subjects, all studies being conducted by a double-blind method.[2,3] The degree of reaction has varied, but symptoms have been induced in all subjects. On three occasions taraxein with activity below threshold was given to human volunteers without the production of observable symptoms. Taraxein has been tested well over 200 times in monkeys. Monkeys with chronically implanted cortical and sub-cortical electrodes are our standard method of assay. We have noted a direct relationship between the effect in the experimental animal and in the degree of symptoms displayed by human recipients receiving the same substance. Also on four occasions we injected 400 ml. of schizophrenic plasma into each of four nonpsychotic volunteers,[3] each time producing mild schizophrenic symptomatology; more specifically symptoms such as lessening of facial animation, depersonalization, blocking and thought deprivation. A similar injection of normal plasma produced no such changes.

Earlier studies were conducted with prisoner volunteers whose psychiatric sophistication was virtually nil; some of them displayed intellectual curiosity about the experiment. The subjects were carefully screened beforehand by two psychiatrists. Volunteers with family history suggestive of mental illness were eliminated. All of the prisoners fall into the diagnostic category of dis-social reactions, having acted out in many ways against society, but showing little in the way of guilt or symptoms themselves. These prisoner volunteers, as with all subjects, upon receiving an injection of taraxein showed characteristically an impairment of their thinking processes. There was marked blocking, disorganization, and fragmentation of thought. They showed impairment of concentration. They said such things as, "I can't think . . . my thoughts break off . . . my mind is blank." They usually looked dazed and out of contact, with a blank look in their eyes. They became withdrawn and had a lessening of animation and facial expression. Their attention span was markedly shortened with an increase in reaction time. Subjects commonly said that they had never experienced such feelings before. The only impairment of memory was during the profound stupor and later recall was excellent except for this period. The sensorium has been clear with the exception of some clouding in severe catatonic reactions. We have seen these volunteers develop paranoid symptoms; including referential ideation, suspicion and auditory hallucinations. Also, we have seen an overt catatonic picture with posturing, negativism and mutism. In no case did injection of one of the substances other than taraxein produce such a constellation of symptoms. In later work we have utilized Bulbocapine and D-LSD-25 as positive controls, again not finding the symptoms obtained with taraxein.

Taraxein has been administered to three schizophrenic patients in remission.[3] One was given a very active dose of taraxein which produced an intensive reaction lasting four days. This time span was more prolonged than in the non-psychotic volunteers. A second schizophrenic developed a clear-cut reaction from a dose of taraxein which induced only an extremely mild response in a nonpsychotic individual. Our experience with administration of taraxein to schizophrenic subjects at this time is neither consistent nor clear-cut.

Dramatic as these symptoms are, the reporting subjects are limited in their introspective and reporting abilities. Accordingly it is significant and we would like to present, in detail, the reported reactions of a psychiatrist, who received the substance. Incidentally the taraxein received by this person was processed in a laboratory other than our own.

The subject, as reported by Dr. Harold I. Lief,[4] was a 27 year old psychiatric resident, who had been in analysis for a year and a half and reported his observations in the 175th session, the day after he received taraxein. He reported that immediately after injection he thought he had received normal saline, but within about five minutes found his thinking slowed and foggy. He wondered whether he

was being tricked into an hysterical reaction and had ambivalent feelings as to whether he should tell the doctor who had administered the solution that he had a reaction or if he should keep on talking and perhaps bluff his way through. The subject reported that the first real indication that he wasn't functioning well, was when he suddenly forgot where his arms were, noticing that he had placed them outstretched in a fixed position and had left them there for several minutes. He then became guarded, saying that at times he couldn't think of anything to say and couldn't carry on a conversation. He stated that he tried to talk on a superficial basis. He reported a rather funny feeling in his face. "I kept feeling for my lips as if they weren't there." After the acute phase was over, some 45 minutes later, as he was eating lunch with the rest of his colleagues, the subject reported that he felt different from everyone, as though he was an observer or outsider. He reported that about an hour and 20 minutes after the injection he felt himself coming out of this abnormal state.

The physician who administered the injection, Dr. Charles Feigley, soon noted that the patient was sitting with his arms flexed in what seemed to be an uncomfortable position and Dr. Feigley was able to extend the arms without any resistance or waxiness on the part of the subject. Dr. Feigley said that he had the feeling that there was something wrong with the subject and he kept wanting to get him to talk about what was going on. He felt that the subject was somewhat belligerent and seemed to be self conscious and at times was silent, uncomfortable and fidgety, closely scrutinizing the observer. On several occasions the subject glanced up quickly and made comments about how closely he was being watched. He glanced furtively at the microphones and at the two-way mirror. The examiner felt that the patient was trying to tell him something while he fiddled with a small gadget which was nearby, that he was trying to say that there was some hidden meaning to the microphones or this gadget. The observer reported that the subject looked emotionally flat and that his facial musculature sagged. Later he seemed to want to be close to the observer, and once he asked him how he looked. Dr. Feigley felt, as he walked with the subject some 35 minutes after the injection, that he was still flat and silent and that he thought of him as a non-entity. For lunch the subject displayed none of his usual comments about food, picked at it and throughout the meal looked out the window at the top of a building opposite.

This subject, like previous volunteers, exhibited blocking of thought processes, autism, and an emotional flattening; the Bleulerian[5] description of the primary symptoms of schizophrenia.

Summary

We have described the clinical effects noted in humans when administered taraxein, a large protein molecule isolated from the blood of schizophrenics. We feel the symptoms which are produced by rapid intravenous injection of this substance, to be characteristic of schizophrenia and not similar to the effects obtained from injection of positive control substances such as Bulbocapine or D-LSD-25.

REFERENCES

1. Heath, R. C., Leach, B. E., Martens, S., and Cohen, M.: Studies in Mind-Brain Relationships, Behavioral Changes with Administration of Taraxein, a Substance Extracted from Schizophrenic Serum. Read at the 112th annual meeting of the American Psychiatric Association, May, 1956, Chicago, Ill.
2. Heath, R. G., Martens, S., Leach, B. E., Cohen, Mr., and Angel, C.: Effect on Behavior in Humans with the Administration of Taraxein. *Am. J. Psychiat.*, 114:1, 1957.
3. Heath, R. G., Martens, S., Leach, B. E., Cohen, M., and Feigley, C.: Behavioral Changes in Nonpsychotic Volunteers Following the Administration of Taraxein, The Substance Obtained from Serum of Schizophrenic Patients. *Am. J. Psychiat.*, 114:10, 1958.
4. Lief, H. I.: The Effects of Taraxein on a Patient in Analysis. *Arch. of Neurol. & Psychiat.*, 78: 624-627, 1957.
5. Bleuler, E.: Dementia Praecox or the Group of Schizophrenics, translated by J. Zinkan. New York: *International University Press*, 1950.

Prognostic Value of the Mecholyl Test

A. HOFFER, M.D., and M. J. CALLBECK

Introduction

Funkenstein and his collaborators[1-4] describe a test of the autonomic nervous system which they found allowed them to predict the success or failure of ECT. In the original account, the test depended upon a response to adrenaline as well as to methacholine U.S.P. (mecholyl). But later this first part of the test was dropped. It now consists of measuring the changes in systolic blood pressure following 10 mg. of mecholyl. Weckowicz[7] showed that the test result could be reproduced on two different occasions in the same subject and noted that since there was no diurnal variation in most of the patients tested, it appears that it does not matter at what time of day it is administered.

The results of confirmatory studies attempted since the original report have been conflicting. In 1953 as part of our research program, we began to accumulate data from mecholyl tests. This paper gives the results of our six year study.

Material and Method

Our sample consisted of 211 patients. The mecholyl test was given at 1:30 P.M. in the way Weckowicz describes. Of these patients 65 received ECT and these will be examined separately. Patients tested were from the psychiatric wards of the General Hospital, Regina and the University Hospital, Saskatoon, Saskatchewan, and included all diagnostic groups.

The mecholyl tests were done by resident research psychiatrists and one of us (M.J. C.) a few days after admission and before diagnoses were made. The test results were not revealed to the clinical staff of these units and so could not be used as indications for treatment. Treatment included ECT, psychotherapy, milieu therapy and medication. The mean duration of hospitalization was between four and five weeks.

The response to treatment was listed as improved or unimproved by the psychiatrist in charge of the patient. This was checked by follow-up in the community. If a patient discharged as improved required readmission within a few days to weeks, he was reclassified unimproved.

The cases were divided into three groups as follows (areas measured by planimeter):

1. Hyper reactor, i.e. area +0.16 sq. inch and over;
2. Normal reactors, i.e. area +.15 to —0.89.
3. Hypo reactors, i.e. —0.90 and less.

There are (or were) three diagnostic groupngis: (a) schizophrenics, (b) neurotics, psychopaths and others, and (c) depressions.

Results and Discussion

1. *The Relationship of Mecholyl Response to Treatment Response.*

The frequency distribution of mecholyl response to treatment is shown in Table 1. This data shows there is no significant relationship between mecholyl and treatment response for all psychiatric treatments. That there is no prognostic value in this test for patients given ECT is shown in Table 2.

TABLE 1

Frequency Distribution of Mecholyl Response to Treatment

	Response		
	Hyper	Normal	Hypo
Improved	27	50	52
Not Improved	19	36	27
N=211	$X^2=1.17$		P>.05

TABLE 2

Frequency Distribution of Mecholyl and Treatment Response to E.C.T.

	Response		
	Hyper	Normal	Hypo
Improved	9	16	15
Not Improved	4	10	11
N=65	$X^2=0.49$		P>.05

2. *The Relationship of Mecholyl Response to Weight and Sex.*

In the atropine test,[6] using 3 mg. of atropin, response varies with weight. That there

This research was supported by National Health Grants, Ottawa and the Rockefeller Foundation, New York under the auspices of the Saskatchewan Committee on Schizophrenia Research.

From Department of Public Health, University Hospital, Saskatoon, Saskatchewan.

is no such response to the mecholyl test is shown in Table 3. Neither does the response differ with sex. (Table 3.)

TABLE 3

Frequency Distribution of Mecholyl Response and Weight, Sex and Age

	Response		
	Hyper	Normal	Hypo
To 130 lbs.	20	27	33
Over 130 lbs.	26	59	46
N=211	$X^2=2.66$		$P>.05$
Male	24	41	28
Female	22	45	51
N=211	$X^2=4.07$		$P>.05$
To 30 years	35	58	43
Over 30 years	11	28	36
N=211	$X^2=6.52$		$P<.05$

3. *The Relationship of Mecholyl Response to Age.*

Gellhorn[5] found that with older patients the proportion giving a hypo response increased. We have confirmed this. (Table 3.) In the younger age group, one third of the responses were hypo. In the older age group, one half responded this way.

4. *The Relationship of Mecholyl Response to Diagnosis.*

Funkenstein and his collaborators reported the mecholyl response predicted the response to ECT. However, it is possible that diagnosis must be considered. It is known that depression runs a limited course in time, whereas in schizophrenia the outcome tends to be more grave. Also patients with depression as a rule respond better to ECT than do schizophrenic patients. Therefore, the difference between the results in this group and the Funkenstein group may be due entirely to the difference in the patient sample. The composition of this group and the response to mecholyl is shown in Table 4.

TABLE 4

Frequency Distribution of Mecholyl Response and Diagnosis

	Response			
	Hyper	Normal	Hypo	Total
Diagnosis				
Schizophrenic	21	40	45	106
Neurotic and Psychopathic	12	32	28	72
Depression	10	13	3	26
N=204*	$X^2=10.86$		$P<.01$	

*Seven patients who did not fit into this diagnostic classification were excluded.

Our group contained a very large proportion of schizophrenic patients. They showed a relatively larger hypo response than did the small group of depressions. Only about 10 per cent of the depressions had such a response compared to 40 per cent for the other groups.

The discrepancy between our data and Funkenstein's may be due to our having more schizophrenics in our sample. The combination of spontaneous remission and response to ECT is higher in depression than in schizophrenia. So that if contrary to his belief, diagnosis must be considered then the fact that our patients contained more schizophrenics than his would make our results different. If this is so, while it accounts for the difference, it greatly reduces the usefulness of the test, for clinical experience suggests that depressed patients are more responsive to ECT.

Conclusion

The mecholyl test does not predict the success or failure in treatment.

Acknowledgment: The mecholyl tests were made by Drs. Zeldenrust, Smith and Chwelos.

REFERENCES

1. Funkenstein, D. H., Greenblatt, M., and Solomon, H. C.: Autonomic Nervous System Changes Following Electric Shock Treatment. *J. Nerv. and Ment. Dis.*, 108, 409, 1948.

2. Funkenstein, D. H., Greenblatt, M., and Solomon, H. C.: A Test Which Predicts the Clinical Effects of Electric Shock Treatment on Schizophrenic Patients. *Am. J. Psychiat.*, 106, 889, 1950.

3. Funkenstein, D. H., Greenblatt, M., and Solomon, H. C.: Autonomic Changes Paralleling Psychological Changes in Mentally Ill Patients. *J. Nerv. and Ment. Dis.*, 114, 1, 1951.

4. Funkenstein, D. H., Greenblatt, M., and Solomon, H. C.: An Autonomic Nervous System Test of Prognostic Significance in Relation to Electroshock Treatment. *Psychosom. Med.*, 14, 5, 1952.

5. Gellhorn, E.: Physiological Foundation of Neurology and Psychiatry. Minneapolis, *Univ. of Minn. Press*, 1953.

6. Hoffer, A., and Callbeck, M. J.: Differential Response of Schizophrenic and Other Psychiatric Patients to Atropine. *To be published*, 1959.

7. Weckowicz, T. E.: Reliability of Mecholyl Test. *Arch. Neurol. and Psychiat.*, 76, 109, 1956.

Color Analysis of the Pyramid Test

P. O. O'Reilly, M.B., B.Ch., and Duncan Blewett, Ph.D.

The color test as devised by the Zurich psychologist, Pfister, has been used as the foundation for continued scientific research on an analysis of the factors determining the choice of colors. A. Friedman[1] reports that blues, reds, and greens constitute 50% of the colors normally chosen. Reds, yellows and orange generally represent about 35% of colors chosen. H. Hiltman[2] and R. Heisz investigated color preferences of normal, TB, schizophrenic, manic depressive and epileptic subjects. They state that each of these groups show a "color syndrome rather than a preference for an individual color. The normal combination is blue-red-green as main colors, yellow-violet-brown-orange as accompanying colors and black-grey-white as subsidiaries. For non-normal subjects, violet was the first choice, appearing in the range of blue-red-green; preferences for green was accentuated and blue and red received less preferences." Although the test as used by Pfister was primarily a diagnostic device based upon the presence or absence of white it may be possible to effect a further differentiation of diagnostic groups on the basis of the color syndromes suggested by Hiltman and Heisz. From their data the following hypotheses are suggested. (1) When the Pfister pyramid is administered the non-normals will show a significantly higher preference for violet than normals, (2) that they also will show a significantly higher preference for green and lower preference for red and blue. It is the purpose of this paper to investigate the color preferences and color syndromes of three groups, normals, schizophrenics and non-schizophrenics.

Description of the Test

The test is to arrange squares of paper (2.5 cm) in 24 shades of 10 standard colors in the space of a previously drawn blank pyramid of 15 squares. In the test material the percentage of white was increased by 100%. This was done because instead of asking the patient to construct three pyramids as other investigators had done it was felt that the construction of one pyramid to be adequate for the study and that white should be obvious enough not to force the subject to search for it. The following instructions are given. "Please make a beautiful pyramid by picking out any colored squares out of the box and glue them on the pyramid in any position that you like." When the patient has completed his pyramid it is held up at a distance of ten feet and the patient is asked, "Do you like the pyramid or would you like to change any color." If he wants to make any changes it is returned to him. If white has been picked in the original selection it is noted if he changes his white selection, other color changes are not recorded. The significance of the selection of white is reported in another paper.[4]

Subjects

The subjects included 65 consecutive admissions to a mental hospital. Diagnosis was made by members of the medical staff of the hospital in conference. Forty three of the subjects were diagnosed as schizophrenic. Of the 22 diagnosed as non-schizophrenic, ten were diagnosed as psychotic, ten as psychoneurotic and two as pathological personalities. The research staff were unaware of the clinical diagnosis given on any case. Normals consisted of a group of 48 student nurses recently admitted to the training school and were tested in a group situation. While the group was cautioned about being influenced by the behavior of other people it seems very likely that such influence existed none the less. In this group setting the subject took a handful of colored paper squares from a large container. Their initial selection therefore undoubtedly played a role in the colors they utilized. Despite these short-comings it was felt that the data obtained would be adequate to denote specific trends.

From Research Division Saskatchewan Hospital, North Battleford, Sask., and Pyschiatric Services Branch, Department of Public Health, Regina, Sask.

Method

The pyramid test was administered to all 113 subjects. Following the completion of the test each time a color was utilized by the subject it was scored. The accompanying tables are the results of the data obtained.

TABLE 1

Color Preferences by Diagnostic Categories

Color	Schizophrenics (N 43)		Non-Schizophrenics (N 22)		Normals (N 48)	
	Total Choices	% of Choices	Total Choices	% of Choices	Total Choices	% of Choices
Green	121	18.76	72	21.81	133	18.47
Blue	118	18.29	56	16.96	121	16.80
Red	88	13.64	35	10.60	94	13.05
Yellow	72	11.16	56	16.96	80	11.11
Violet	58	8.99	43	13.03	61	8.47
Orange	42	6.51	39	11.80	76	10.55
Brown	52	8.06	15	4.54	63	8.75
Black	28	4.34	8	2.42	42	5.83
Grey	14	2.17	6	1.81	23	3.19
White	52	8.06	0	—	27	3.75
Totals	645	99.98	330	99.93	720	99.97

TABLE 2

Significance of Differences in Color Preferences of Diagnostic Groups

Difference Color	X^2 Schiz. Non-Schiz.	X^2 Schiz. Normal	X^2 Normal Non-Schiz.
Green	.2142	.4313	.0036
Blue	.2142	.4313	.0036
Red	1.5961	.0881	1.1039
Yellow	5.6100*	.0007	5.5992*
Violet	3.4399	.1054	4.7423*
Orange	7.3932†	6.4376	.3300
Brown	3.9312*	.1911	5.4181*
Black	2.1677	1.4792	5.5169
Grey	.1316	1.3130	1.5194
White	26.6046†	10.9296	12.3840†

*Significant at the .05 level of probability (X^2 3.841)
†Significant at the .01 level of probability (X^2 6.635)

Discussion

Color preferences by diagnostic categories are presented in Table I and the significance of differences in these preferences are set forth in Table II. These data provide the evidence against which we can check the two hypotheses.

(1) Non-normals will show a significantly higher preference rate than normals for violet. This hypothesis is supported in part. The non-schizophrenic patients select violet more frequently than normals. This difference is significant beyond the 5% level of probability. However no difference was found between schizophrenics and normals as regards preference for violet.

(2) More normals will show a significantly higher preference for green and lower preference for red and blue. This hypothesis is not substantiated by the findings.

Although the hypotheses are not substantiated, there are certain features of the distribution of color preferences which merit attention. It will be noted that the normal combination is green-blue-red-yellow as main colors, orange-violet-brown as accompanying colors and black-white-grey as subsidiaries. While this does not accord directly with the findings of Hiltman and Heisz in that the colors do not follow in the same order of preference, nevertheless, the general configuration is the same in terms of the colors which fall into the main, accompanying and subsidiary classification.

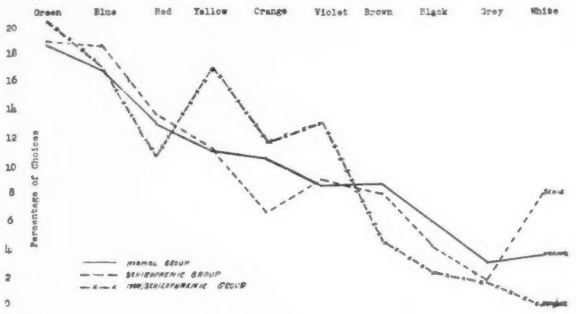
The non-schizophrenic patients differed from the normal group in terms of their preference for violet and yellow and their relative dislike for brown and black (all of these differences being significant at the 5% level). One difference between these groups was significant beyond the 1% level of confidence. This was the relatively more frequent use by normals of the color white. This may in part result from the previously mentioned mode of administration used for the normals.

The non-schizophrenic group differed from the schizophrenic group in that the former showed a greater preference for yellow (5% level), orange (1% level) and greater dislike for brown (5% level) and white (1% level).

The schizophrenic pattern of preference followed that of the normals rather closely there being significant differences only in that the schizophrenics showed greater dislike for orange (5% level) and a more frequent choice of white (1% level).

The plotting of preferences by color and diagnostic category as presented in figure A very strongly suggests that in color prefer-

ences as assessed by behavior on the Pfister Pyramid Test indicates little evidence to support Hiltman and Heisz's concept of color syndromes.



Summary

Two hypotheses were investigated using the Pfister Pyramid Test. It was hypothesized that (1) Non-normals will show a significantly higher preference than normals for violet, and (2) non-normals will show a significantly higher preference for green and lower preference for red and blue.

With regard to the first hypothesis non-schizophrenics showed significant preference for violet (5% level), schizophrenics did not. The second hypothesis was not supported by the data obtained. Of the thirty differences obtained by using ten colors for three diagnostic categories, seven were found significant at the 5% level and four at the 1% level. No evidence to support the concept of color syndromes was obtained.

Acknowledgments: We wish to thank Dr. Demay, superintendent, and the staff of the Saskathcewan Hospital for their co-operation and help. Thanks is also due to R. Kilpatrick, research nurse. Approved by the Saskatchewan Committee on Schizophrenic Research. Supported by the Department of National Health and Welfare, Canada.

BIBLIOGRAPHY

1. Friedman, A.: Fischerweg 6, Biel. test des pyramids en couleure (Pfister-Heisz). *Rorschachianna* (Zurich) 1953, 1/4 (343-359).
2. Hiltman, H., and Heisz, R.: Der psychologisch-diagnostische Wert von Farbreaktionen. Schweiz. Z., *Rev. suisse Psychol.*, 1950, 9/4 (441-462).
3. Seeger, E. K.: Personlichkeitstest und Verifzierung der Testergebnisse. *Psyche* (Heidelberg), 1954, 7/12 (161-172).
4. O'Reilly, P. O., Holzinger, R., and Blewett, D.: The Pfister Colored Pyramid Test. (In press.) *J. of Nerv. & Ment. Dis.*

Survey of Modified Electroshock Therapy

OSCAR ROZETT, M.D.

A common and unpleasant complication of electroconvulsive therapy is fracture, especially of the vertebrae. Reports in the literature indicate that fracture occurs in substantially more than 20 per cent of cases.[1] Lingley and Robbins[2] reported fractures in 23 per cent of their cases, Nyby[3] in 14 per cent, and Meschan, *et al.*,[4] in 39 per cent. The powerful muscular exertion during the convulsion constitutes a great strain upon the patient. For this reason it has been inadvisable at times to employ such treatment, despite strong psychiatric indications. The purpose of this paper is to show that the use of muscle relaxants in minimal dosages modifies the convulsion to an extent that avoids skeletal damage, but permits a recognizable convulsion.

The apparatus we now employ operates on 110 volt, 60 cycle alternating current. The controls consist of a voltage control ranging from 70 to 170, a time control ranging from .1 to 1. second, and a glissando timer ranging from .7 to 1.5 seconds. This is essentially the same as an alternative machine, that we use, in which the glissando is automatic and non-variable. Our applications usually start at 90 volts for one second with the glissando timer set at 1.25 seconds. We have tried other machines and other currents but we have not found them superior in any way to the method of treatment described above. By lowering the voltage to 90 and increasing the time to one second, we give the patient a minimal jolt as compared with the response to a setting of 130 volts with a time of .3 second, for example. If our initial setting does not result in a convulsion, we increase the voltage to 100 and repeat the treatment, often doing so a third time if we work quickly, i.e., within a 30 to 40 second period. After that time the effect of the

muscle relaxant, succinylcholine in this case, diminishes and it is not advisable to apply further treatment.

During 1954 and 1955 unmodified electroshock therapy was administered at Fair Oaks Hospital in Summit, N. J. Muscle relaxants such as Curare and Flaxedil were used only where there was some definite clinical indication. During these years we experienced fairly frequent occurrence of compression fractures of one or more vertebrae. In 1954, for example, we had 22 compression fractures that were directly attributable to our treatments. In 1955 there were 26 such fractures. In 1956 we began using succinylcholine in conjunction with electroconvulsive therapy.

The selection of patients and their preparation are exactly as in the past. Since our treatments are administered between 11 a.m. and 12:30 p.m., the patients are given toast and coffee at 7:30 in the morning, having received neither food nor drink since the preceding midnight. All patients receive one-fiftieth grain atropine intramuscularly one-half hour prior to treatment.

Succinylcholine deteriorates in a few minutes in an alkaline solution of Surital. Therefore, a freshly prepared mixture is injected intravenously. The dosage is calculated in the following manner:

We use .1 cc. succinylcholine for each 20 pounds body weight as the basic dose and then make the following modifications:

If the patient is young and muscular, or simply heavily muscular, we add from .1 to .2 cc. succinylcholine;

If the patient is old with poor musculature, or simply an individual with poor musculature, we subtract .1 cc. from the basic dose.

We employ succinylcholine in a flexible manner, adjusting the dosage for each individual where necessary to take into account such conditions as old compression fractures, hypertrophic osteoarthritis, poor myocardium, spinal fusions, osteoporosis, etc.

Dosages varied between a minimum of .4 cc. succinylcholine and a maximum of 1.6 cc. The average dose for female patients we have found to be .6 cc. or 12 mmg., and for male patients .8 cc. or 16 mmg.

After the succinylcholine is mixed with the Surital, the patient is given the injection rapidly (in about 15 seconds). We have found that a waiting period of 15 to 30 seconds insures good relaxation in the vast majority of patients. If the modification of the convulsion is not satisfactory, that is to say, if it is not a plus one or a plus two convulsion, the dosage is altered. The degree of reaction is classified as follows:

One plus: When a minimal convulsion occurs without movements of the extremities.

Two plus: When some movement of the extremities occurs but little force is required to hold down the patient.

Three plus: When movement of the extremities occurs and considerable force is required to hold the patient.

Four plus: When the convulsion appears to be entirely unmodified by the muscular relaxant.

Oxygen is kept immediately available and patients are routinely resuscitated with alternating positive and negative pressure until normal breathing is resumed. By using minimal dosages of succinylcholine we have had negligible difficulty due to apnea. We have found the use of a pillow under the patient's back unnecessary but we do use a small pillow under the patient's cervical spine. A protective mouth gag is inserted to prevent tongue or lip biting and to protect the teeth. Immediately following the treatment a Guedel airway is inserted and resuscitation is commenced.

During 1956 and 1957 we treated a total of 739 patients with an average age of 47.3 years we administered 7,363 treatments.

All patients were x-rayed prior to therapy. There were 565 normal spines. Among our patients, we found the following:

Old compression fractures of one or more vertebrae—54 cases.

Kyphosis—26 cases.

Hypertrophic osteoarthritis—99 cases. Of these 39 were severe, 43 moderate, and 17 were mild.

Osteoporosis—24 cases.

Surgical spinal fusion—4 cases.

Spondylolisthesis—6 cases.

Ankylosing spondylitis—2 cases.

Hypertension—176 cases.

Poor myocardium—125 cases.

History of coronary occlusion—11 cases.

Patients receiving digitalis—15 cases.

Coronary sclerosis on EKG—36 cases.

Thrombophlebitis just prior to treatment—2 cases.

Multiple sclerosis—2 cases.

Muscular dystrophy—1 case.

Paget's Disease and pathological fractures just prior to treatment—1 case.
Pregnancy—1 case.
Cerebral aneurysm—1 case.

We would like to point out that of the total number treated, 182 patients were above sixty years of age and, of these, 47 patients were seventy years and older, with two patients exceeding eighty years of age.

One patient died of a coronary thrombosis two weeks after the last electroshock treatment. This patient was a 64 year old hypertensive who developed symptoms of coronary occlusion about twenty-four hours after the last treatment was administered.

This survey covers a full two years. We encountered during this period of succinylcholine-modified electroconvulsive therapy not a single compression fracture. As a matter of fact we have just completed a third year of such therapy, again without fractures of any sort.

We do not routinely x-ray each patient after he has completed his course of electroshock therapy. We did not do this in 1954 and 1955, when we encountered 22 and 26 compression fractures respectively. At that time x-rays were taken only when patients complained of pain. We have continued this procedure during years 1956, 1957, and 1958, and routinely x-ray all patients who complain of pain of any sort following electroconvulsive therapy. According to Funkhouser and Davis,[5] 70 per cent of patients suffering fracture incurred during electroconvulsive therapy complain of pain. In view of this and taking into account our own experience, we feel that our results are of value.

Using succinylcholine in minimal dosages obviates the need of an anesthesiologist and also reduces the possibility of prolonged apnea. By using small doses of Surital we increase the safety of the treatment. We administer Surital only in sufficient dosage to reduce the anxiety which we encountered when we used succinylcholine alone.

Of the 7363 treatments administered in 1956 and 1957, we found only 160 occasions, or 2 per cent of the total, when a four plus reaction was produced, and in these cases the dosage of succinylcholine was increased in order to achieve a two plus reaction.

In 462 treatments, or 6 per cent of the total, we found three plus reactions. In 5360 or 73 per cent of the total, we achieved a two plus reaction, and in 1,380 or 19 per cent of the total, a one plus convulsion resulted. In other words, in 6,740 or 92 per cent, a one plus or two plus reaction was achieved. And in 622 treatments or 8 per cent, an undesirable three plus or four plus reaction resulted. Needless to say, we were fortunate that in none of these cases did the patient complain of backache nor, so far as we could determine, suffer any injury. We consequently feel that some amount of beneficial modification is achieved, even in those cases where a three plus or four plus convulsion occurred. And we are firmly convinced that modification of the convulsion with succinylcholine does not change the therapeutic result. In fact, we probably get better results due to the fact that we do not have to interrupt treatments because of a fracture.

Conclusions

(1) We feel that fracture complications can be almost entirely eliminated as a hazard of electroconvulsive therapy.

(2) Succinylcholine in minimal doses should be used for every patient who receives electroconvulsive therapy, irrespective of age or physical condition.

(3) Desirable modification of the convulsion is achieved with the use of succinylcholine in minimal doses, even where an infrequent four plus convulsion is observed.

Acknowledgments: I wish to thank the staff physicians, Drs. Paul Singer, the late Monroe E. Neuman, Ernestine Sokal, and Elizabeth Rozsa, for their cooperation in the use of the technique described in this paper. They concur in the conclusion that moderate modification of electroconvulsive therapy has rendered the treatment far safer.

Acknowledgment is also due James W. Hammett, Jr., for his assistance in compiling the statistics for this paper.

REFERENCES

1. Noyes, A. P., and Kolb, L. C.: *Modern Clinical Psychiatry,* 5th Ed., p. 611.
2. Lingley, J. R., and Robbins, L. L.: Fractures of the Spine During Electro-Shock Therapy. *Radiology,* 48:124, 1947.
3. Nyby, O.: Incidence of Fractures in Electro-Shock Therapy. *Nord. Med.,* 40:2162, 1948.
4. Meschan, L., et al.: Convulsive Fractures of the Dorsal Spine Following Electro-Shock Therapy.
5. Funkhouser, James B., and Davis, Hiram W.: A Critical Survey of Fifty Spinal Fractures Due to Electric Shock Treatments. *J. of Nerv. and Ment. Dis.,* 116:131, August 1952.

Evaluation of Deprol in Psychiatric Out-Patients

(Comments on a Double-Blind Technique)

DONALD D. LATHROP, M.D.

This is a report of a drug study.* The drug under consideration is Deprol, which is a combination of meprobamate 400 mg. and benactyzine 1 mg. The purpose of the study is to determine the effectiveness of Deprol in the treatment of certain psychiatric patients, particularly ambulatory or pseudoneurotic schizophrenics, such as attend a large municipal psychiatric clinic. In addition, some observations on drug-study technique are made.

Method

In general, the design of the study was to administer a standard dosage of drug to randomly selected patients and then evaluate the change in the patients' feelings or symptoms. At the conclusion of the study, changes were correlated with drugs to learn what, if any, effects the drugs produced.

The investigator is a psychiatric resident with previous research experience. The study was conducted in the Tulane Psychiatric Clinic of the Charity Hospital of Louisiana at New Orleans. This clinic meets two mornings a week, once for whites and once for Negroes. The daily case load varies from eight to fifteen patients, the majority of whom are on the brink of disaster psychologically and socially. Nearly all are medically indigent to the extent that they get their medicines free through social agencies. Therapy in this clinic includes environmental manipulation, support, guidance, exhortation, pharmacotherapy, and insight therapy.

The patients for this study were selected from the normal case load. Some had been previously seen. Most had been treated in either the recent or remote past with other drugs, usually by other therapists. Some had been hospitalized, some had had ECT.

Each patient was selected on the basis of his need for drug therapy. Many patients, for example, presented a long history of somatic complaints. Drug therapy is indicated both for reduction of underlying anxiety (which is expressed through the somatic symptom) and for the psychotherapeutic effect of the doctor giving the patient some kind of pill to help him.

The problem of concurrent psychotherapy must be mentioned. It was initially planned to do no psychotherapy on these patients during the study. This proved to be unrealistic. Simply conducting repeated mental status exams by interview technique constitutes some kind of psychotherapy, in my experience. Therefore, each patient was treated as indicated in the time available, treated in the same manner as he would have been treated in the absence of the drug study. My subjective impression of the effects of the doctor-patient relationship on the patient's progress was recorded and included in the over-all evaluation. This free use of concurrent psychotherapy is justified by the fact that the average practitioner inevitably dispenses some "psychotherapy" along with his prescription.

The only other criterion consciously employed in selecting patients was trying to include patients who would return each two weeks for at least two months. However, this proved difficult, and only 60% of those who started were completed. This is consistent with previous experience in this clinic.

Once it was decided to include a patient in the study, a data sheet was filled out. This included all of the recommended identifying data[1] as well as a mental status. The latter totalled fifty-eight items which were listed for grading. These were listed under the main headings of Affect, Association, Autism, Ambivalence, Mood, Anxiety, Defenses, Psycho-motor sensory, and Psychophysiologic. Items were graded on a scale from zero to five with five representing most severe or deviant. For example, a patient with no hallucinations would be graded zero;

From Dept. of Psychiatry, Tulane University and Charity Hospital.

occasional experiences of hearing his name called might be graded one; frequent but unannoying voices might be three; constant voices of which the patient complained bitterly would be rated five.

Obviously, this rating system is quite subjective. It proved extremely difficult to use in practice. Therefore, an over-all rating described below was used for assessing drug effects and no statistical use was made of these ratings on individual items of mental status.

Following the completion of the data sheet and initial mental status, the patient was given sixty plain white tablets in a box marked, "Take one four times a day." The boxes were marked with a code number which was recorded on the patient's chart. The code, which identified the drug in each box, was kept from the investigator until completion of the study. The patient was told that these pills were to help him. He was instructed to return in two weeks and to bring the box back with him. The purpose of having the box returned was to check on the number of pills taken. If the pills were taken according to directions, there should be four left at the end of two weeks. In the majority of the cases, the patient returned the box *empty*. I suspect that this means the patient found he had some pills left and emptied them out to avoid displeasing the doctor. About 20% of the time, there were more than four pills in the returned box. Occasionally, the patient had taken as few as half of the pills. Thus, this procedure served as a partial safeguard against spurious conclusions.

The drug to be evaluated contains two active components. Therefore, it was necessary to test the combination and each of the components separately in order to make any valid statement about the effects of the drugs. Each patient was his own control. He received the combination, one of the two component drugs, and a placebo. It would have prolonged the study too much to give each patient both components. Initially, only the Deprol (D), meprobamate (M), and placebo (P) were available in the identical tablets. The drugs were distributed so that each patient had an equal chance of starting on D, M, or P. Also, each possible combination was equally available, so that patients received drugs in each of the possible orders: D-M-P, D-P-M, P-D-M, P-M-D, M-P-D, and M-D-P. When the benactyzine became available in identical tablets, it was set up in the same way. Meprobamate tablets contained 400 mg. and benactyzine tablets were 1 mg.

When the patient returned in two weeks, he was again rated on the mental status. He was also rated on over-all improvements as follows:

1—no improvement;

2—slight improvement: some beneficial effects noted but as yet not enough to warrant further use of the drug;

3—moderate improvement: favorable results but patient seeking further relief;

4—marked improvement: symptoms subsided and no longer disturb patient;

5—recovered: symptoms subsided completely both subjectively and objectively; patient now socially productive.

He was also rated on this scale according to his own (subjective) opinion of his improvement. This proved of no practical value since it rarely differed significantly from the doctor's rating.

His amenability to psychotherapy was rated as good, fair, or poor. This also proved of no practical value since it was too crude a measure to be interpreted separately.

A guess was then made by the investigator as to the content of the tablets which the patient had been taking for the preceding two weeks. The "guess" was based upon any cues available, including taste of the drug if the patient complained of it. The purpose of this "guess" was to test the validity of the double-blind technique in this study. (I have long felt that it is not as blind as it is purported to be and wished to test this suspicion.)

Finally, comments were recorded on any other factors which might have influenced the patient's condition during the preceding two weeks—such as being placed on welfare, loss of job, etc. Also noted were any comments the patient had to make about the treatment. (These were often most enlightening—and occasionally amusing. For example, one woman reported that the pills I

gave her were much better than the Miltown she had been buying on a previous doctor's prescription. As you might guess, it turned out that she had been on meprobamate during that test period.) The patient was then given the next box of pills in the sequence and told to return in two weeks.

This procedure was repeated every two weeks until the patient had taken three preparations. After that, a few patients were given double doses (two tablets q.i.d.) of either Deprol or benactyzine. In these instances, the investigator knew the drug being given. The purpose was to see whether increased dosage would be effective where the normal dosage (one q.i.d.) had failed.

The Sample:

Forty-nine patients were begun on drugs. Of these, twenty-nine completed the full course. Of the twenty who were incomplete, nine never returned after their first visit, four quit after the second, and two after the third. This did not seem to be related to the drug they had been given. (Five had gotten placebo, four benactyzine, and three each Deprol and meprobamate.) Three patients were discharged as unsuitable either for failure to return at two week intervals or failure to take the medication. Two patients whom I had been treating for several months were dropped from the study because performance of the mental status rating scale interfered with their psychotherapy by focusing too much attention on symptoms. One other patient was hospitalized elsewhere for intensive study of chronic headaches. She was found to have an elevated spinal fluid protein for which no cause could be found. She had been on meprobamate for a few days at the time she was hospitalized.

For the sake of simplicity, we can conceive of the composite patient as a premenopausal Negro woman who finished grade school, is married, does not work, is severely incapacitated as a result of mild stress, and has been overtly ill for many years with schizophrenic vsymptoms. The details may now be presented.

There were thirteen men and thirty-six women in this sample; this is about average for this clinic. Similarly, the preponderance of thirty-two Negroes over seventeen whites reflects the greater patient population in the Negro clinic. The age range was from 17 to 61, with a mean age of 43. The average grade attained in school was the sixth, ranging from no school up to one year of college. Marital status was as follows: single—fourteen; married—twenty-two; separated — eight; widowed — two; divorced — two. (This represents only current status and does not take account of a large number of previous divorces and remarriages.) Nine of these patients were employed. The duration of the chief complaints was less than two months in eleven patients, less than six months in seven patients, less than a year in six patients, and of several years' duration in the remaining twenty-five.

Precipitating stress was judged subjectively by the investigator and rated as follows: mild—twenty-seven; moderate—seven; severe — three; unknown — twelve. Thus, the group tended to show breakdown under minor stress. Likewise, the degree of psycho-social impairment was rated and tabulated as follows: mild—eleven; moderate—nineteen; severe—nineteen. Thus, the group tended to show marked incapacitation due to the emotional illness.

It is difficult to break the group down meaningfully into diagnostic categories. The diagnosis of pseudo-neurotic schizophrenia is made where the patient presents disorders of affect and association, autistic tendencies, and marked ambivalence. Many patients also had secondary symptoms. These might be called ambulatory schizophrenics. Many of the schizophrenic patients were also depressed or anxious. However, the primary diagnosis was based upon the underlying pathology. Broadly, the diagnostic tabulation includes thirty-three schizophrenics (ambulatory or pseudo-neurotic), five conversion hysterias, six depressive reactions, and five anxiety neuroses.

Results

In an over-all assessment of improvement, *aside from specific drug effects,* about one-third showed good results, one-third fair, and one-third poor. According to diagnostic categories: schizophrenic—five good, six fair, seven poor; depression—two good, three fair, one poor; anxiety and hysteria—four good,

one fair. These results are about what may be expected from non-specific treatment.

Interestingly, it is not difficult to predict which patients will improve. For each patient, there was a predictable prognosis of good, fair, or poor on the basis of the first visit. Of the ten predicted good, nine had good results and one fair. Of five predicted fair, three had fair results, and one each good and poor. Of the fourteen predicted poor, eight turned out that way, five made fair, and only one had a good result. Thus, it would not be at all difficult to select a group who would do well on whatever regime was tried.

You will recall that each patient was rated for over-all improvement, on each visit, on a zero to five scale. Regrettably, these numbers do not correspond to any unit of measurement. Therefore, any statistics based upon these numbers are full of unreliability. The conclusions, therefore, are based upon clinical judgment. The statistics are presented only for the purpose of illustrating some relationships.

TABLE 1

	N	Mean improvement (in rating scale units)	Standard deviation (in rating scale units)
Placebo	31	2.16	1.09
Benactyzine	10	2.00	—
Deprol	31	2.61	1.15
Meprobamate	19	2.84	1.11

The superiority of Deprol over placebo is not statistically significant (this amount of difference would occur once in eight times by chance alone). The superiority of meprobamate over placebo is significant at the 5% level of confidence (t—2.19).

Because of recent interest in using Deprol to alleviate depressed mood, the data under Mood in the mental status were examined. Where depression was a prominent symptom, it had been scored on the zero to five scale. Twelve patients showed an average of two units of improvement of depression while on Deprol. In fourteen patients, placebo and benactyzine produced an average of one unit improvement. Meprobamate produced one unit of worsening of depression on the average in six patients. These are crude data at best, but they agree in spirit with the findings of Alexander.[2]

The effects of these drugs on delusions and hallucinations were not surprising. Three patients showed no effect. There was disappearance of delusions or hallucinations in one instance each while a patient was on Deprol, meprobamate, benactyzine, and placebo.

Side effects were extremely hard to evaluate. No dangerous toxic effects were observed. One patient was taken off benactyzine by a dermatologist because of a rash. However, she had recently had penicillin. To illustrate how difficult it can be to assess side effects, the following undesirable effects were noted and were attributed either by the patient or the doctor to the drug *while the patient was on placebo:* dizziness, insomnia, nervousness, drowsiness, abdominal cramps, nightmares, swelling of breasts (female), and a "zombiish" appearance.

In general, though, it did seem as though Deprol tended to produce drowsiness and occasionally symptoms of postural hypotension. Frequently, the side effects were specific for the patient. For example, one paranoid schizophrenic man reported premature ejaculation while on Deprol. He had never had this symptom before. He also noted that he didn't feel as antagonistic toward people while on Deprol. He finally went back to taking phenobarbital which did not suppress his rage as much, but neither did it interfere with his sexual function. This, I believe, is a psychodynamic rather than a pharmacodynamic side effect.

A very few patients were tried on double doses (two q.i.d.) of Deprol or benactyzine. In one instance on each drug, improvement occurred where there had been none previously and seemed definitely due to the drug.

Another bit of experience on dosage comes from a group of pseudo-neurotic schizophrenic women I am treating in intensive group therapy. For the past year, these patients have been given only Deprol when drug therapy was required. Because they are under constant supervision, they are permitted to set their own dosage level according to their feelings. They have learned

to titrate drug against anxiety. In general, they take two to four tablets for marked anxiety. Sometimes this dose will be repeated every four hours, sometimes not. When there is less anxiety, one or two will suffice. In a panic state, as many as eight tablets were taken without ill effect. One patient, subject to recurrent auditory hallucinations accompanied by subcortical electrical storms, has taken six to eight tablets four times daily for several days without ill effect. This did not obliterate the hallucinations but cut down some on her apprehension. Thus, it seems that the sicker the patient and the greater the anxiety, the higher the tolerance to these drugs.

Discussion

It will be noted that meprobamate alone made a better showing than when it was combined with benactyzine. Although these data are not strong enough to support much speculation, there is a theoretical explanation for this finding. It seems that benactyzine tends to produce mental blocking (thus its supposed value in obsessional neuroses). I believe it also enhances depersonalization. Either of these two effects would tend to make the pseudo-neurotic schizophrenic feel worse, by aggravating already existing subjective sensations. Meprobamate does not usually block thoughts or foster depersonalization. Hence, *in these patients,* meprobamate alone is better than the combination, Deprol. I further speculate that in acutely disturbed patients (such as the group therapy patients) the effects of benactyzine are not noticed because the patient already has plenty of blocking and/or depersonalization. In the chronic patients, such as in the clinic, an equilibrium of sorts has often been attained and the patient may be very sensitive to slight changes induced by even 1 mg. of benactyzine.

The results of trying to outwit the double-blind are fascinating. I was able to guess two-thirds of the time whether the "unknown" pill contained drug or placebo. This is considerably better than would be possible by chance alone. There is nothing to prevent an investigator from doing this unconsciously and simultaneously unconsciously making his results agree with his expectations. Furthermore, there is no protection against this kind of bias in statistical manipulation of data. The only way in which this factor can be controlled is for the investigator to try to guess through the double-blind. His success is then compared with the probability of such guessing and a measure of validity may be obtained. Certainly, one must be alert in reading the literature, and avoid being lulled or comforted by the double-blind technique. It may unwittingly cover an uncontrolled study.

Conclusions

1. Deprol (meprobamate 400 mg. and benactyzine 1 mg.) is not particularly effective in the treatment of out-patient schizophrenics at a dosage of four tablets daily for two weeks.

2. Meprobamate alone produces more overall improvement in such patients. In my opinion, it is superior to Deprol or benactyzine and may be used in doses of 400 to 1600 mg. one to four times daily depending upon the acuteness and severity of the anxiety.

3. Deprol seems to have more anti-depressant effect than benactyzine or meprobamate alone.

4. Deprol has no specific effect on delusions or hallucinations.

5. In dosages of one tablet four times a day, Deprol has no consistent side effects but does produce occasional drowsiness.

6. Drug studies such as this are replete with pitfalls. Patients with a good prognosis may easily be selected. Double-blind techniques are not a guaranteed safeguard against bias. Statistics based upon numbers which have no basis in any unit of measurement are of questionable validity.

BIBLIOGRAPHY

1. Recommendations for Reporting Studies of Psychiatric Drugs. *Public Health Reports,* 72, 638-645, July 1957.
2. Alexander, L.: Chemotherapy of Depression. *J.A.M.A.,* 166, 1019-1023, March 1, 1958.

All drugs used in this study were supplied by Wallace Laboratories, New Brunswick, New Jersey.

Multiple Sclerosis and Rheumatic Fever: Related Diseases

DEWEY K. ZIEGLER, M.D.

It has been repeatedly suggested in recent years that some cases of multiple sclerosis are the result of an allergic reaction of the nervous system to an antigen, although evidence for the hypothesis is by no means abundant.[1-7] Because of the marked tendency for the "allergic diathesis" to manifest itself in different forms in different members of the same family, it seemed possible that there might be, in the families of multiple sclerosis patients, an increased incidence not only of the common allergic disorders, but also of rheumatic fever, a disease generally thought to be the result of allergic tissue reaction to the Group A streptococcus bacillus.[8-10] If such increased incidence were present, the fact might lend support to the "allergic" theory of multiple sclerosis, or furnish clues for further study of the disease, by analogy with the more fully understood rheumatic fever.

It was further speculated that if the allergic diathesis were operative in these two diseases, families with different members showing multiple sclerosis, rheumatic fever, and more generally accepted allergic disorders (asthma, hay fever, eczema) would occur.

Material and Methods

The subjects of our study were 280 multiple sclerosis patients. They either attend a special clinic for multiple sclerosis and were personally examined, or were registered with the multiple sclerosis society of a large city and were reached by mailed questionnaires. In the latter instances the cases were accepted for study only if they had been diagnosed by a neurologist. By this means it was believed that errors in diagnosis, while not completely eliminated, would be reduced to a minimum. I examined 81 patients; data from the remaining 199 patients came from questionnaires, which represented a return of over 80% of those sent out.

The questionnaires asked the patients to note if they had ever had hay fever, asthma, hives, eczema, or other skin allergy, allergy to food or drug, rheumatic fever, or rheumatic heart disease. The patients were asked to give details about any of the illnesses on which they reported. Because migraine headaches are alleged to be of allergic origin, the patients were also asked about headache. The second part of the questionnaire asked the patients to give details about any of these diseases known to occur in any members of their immediate families—parents, grandparents, brothers, sisters or children. Positive answers to these questions were followed up by telephone interviews with over one-half of the patients not personally examined, to verify or amend the data, particularly that concerning rheumatic fever.

Results

A. Rheumatic Fever

The incidence of rheumatic fever in multiple sclerosis families is seen in Table I.

TABLE I

Rheumatic Fever in Patients and Families of Patients with Multiple Sclerosis

	No. of Cases	% of Sample
Patients with history of R. F.	21	7.5
Patients with history of R. F. in sibling	19	6.8
Positive history of R. F. in immediate family (sibling, parent or child)	50	18

Details of findings of allergic disorders in the families will be given elsewhere; however, it was found that 98 or 34.9% of the multiple sclerosis patient population gave a history of one or more immediate family members with asthma, eczema, hay fever, or repeated urticaria.

B. Allergic Families with Multiple Sclerosis and Rheumatic Fever

There were several family histories in which rheumatic fever and other allergic diseases occurred with some frequency. In four cases the patients volunteered the information that both rheumatic fever and multiple sclerosis occurred in siblings. Partial pedi-

From the Division of Neurology, University of Minnesota Medical School, Minneapolis, Minn.

grees of three of these patients are given in Figure 1.

In Figures 2 and 3, partial pedigrees of 10 additional families have been selected to demonstrate the frequent co-incidence of multiple sclerosis, rheumatic fever and allergic disease in the same family. Migraine is included, since there is evidence that it occurs with some frequency in association with other allergic disease; it was diagnosed in these cases since enough details of the headache were given to warrant a supposition that this specific clinical syndrome was present. Included in allergic dermatitis was eczema or severe or prolonged contact dermatitis. Food allergies were not included in this study because of the uncertainty of diagnosing them by history, although they were frequently reported.

Discussion

The view is becoming prevalent that "multiple sclerosis," as now used, refers to a group of diseases which ultimately will be found to be of diverse etiologies. The speculations in the subsequent paragraphs on allergic mechanisms, must be understood, therefore, to apply only to a portion, great or small, of multiple sclerosis patients; they are put forward as a possible one, out of a probable many, etiologic factors.

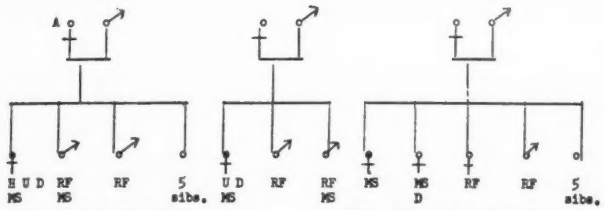
Some clinical characteristics of multiple sclerosis are reminiscent of rheumatic fever. Both illnesses are characterized by transient attacks which may or may not leave permanent tissue damage. Both are common in cold climates and uncommon in tropical ones.[11,12] There is a familial incidence of both diseases although this is apparently more uniform in rheumatic fever than in multiple sclerosis.[13-16]

Both illnesses have been ascribed to a hypersensitivity reaction. For rheumatic fever, this hypothesis has been fairly generally accepted on evidence of its close clinical relations with streptococcal infections, and the immunological responses of the rheumatic fever patient to streptococcal products.[9,17]

The thesis that some multiple sclerosis is the manifestation of an allergic reaction of the nervous system is based on five kinds of data: 1. Analogy of rapidly appearing and disappearing signs and symptoms with similarly rapidly altering allergic phenomena. 2. Cases of transient and sometimes severe neurological signs and symptoms following exposure to allergens, usually food allergens.[18-20] 3. Fairly high incidence, in the serum of multiple sclerosis patients, of positive complement fixation reactions to antigen derived from brain and spinal cord of multiple sclerosis occurring with significant frequency during or immediately following acute allergic episodes.[21-23] 4. The existence of a demyelinating disease, presumably allergic in nature, produced in several species of animals, by using as antigen brain and spinal cord emulsion treated with Freund adjuvant.

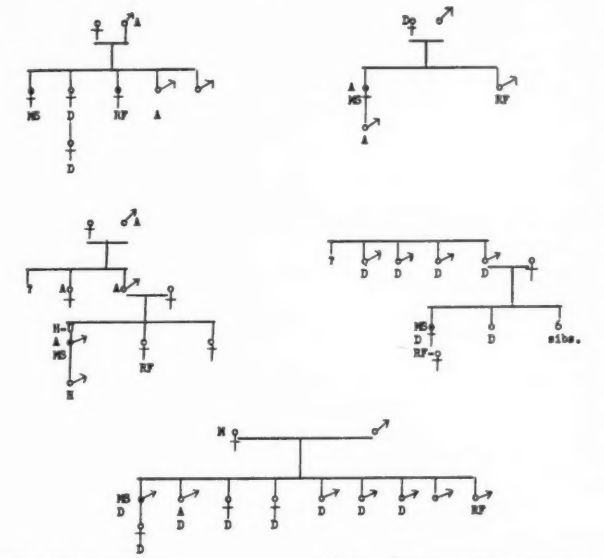
There are at least three possible relationships between rheumatic fever or streptococcal infections, allergic disease, and multiple sclerosis. One is that allergic diseases, multiple sclerosis and rheumatic fever all occur in individuals of a constitutional tendency toward diverse hypersensitivity reactions, and that this tendency has as yet undefined significance in multiple sclerosis. No etiologic link between the three conditions would then be postulated. In favor of this theory is the absence, in most cases, of infection or overt allergic disease preceding attacks of the disease. The evidence as to whether rheumatic fever patients do have a constitutional tendency to other allergic reactions is minimal but suggestive[24-26] despite one study demonstrating failure of rheumatic fever patients to produce antibody to bacterial antigen (other than streptococcus) in excess of controls.[27]

A second possible allergic mechanism, mentioned by McAlpine,[1] is that multiple sclerosis results from "tuberculin" or delayed sensitivity of the nervous system to bacterial infection. It might be postulated that siblings develop rheumatic fever as another manifestation of this bacterial allergy. McAlpine[7] has demonstrated a statistically significant incidence of skin infections immediately preceding attacks of multiple sclerosis. Furthermore, a rise in anti-streptolysin titre has been demonstrated in many cases of multiple sclerosis.[28] The same objections mentioned before might be objected to this theory—the absence of known infections in the vast majority of cases of attacks,



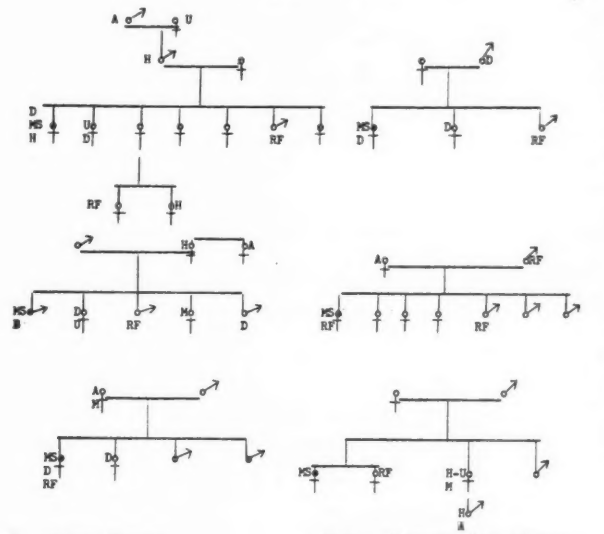
H—Hay Fever
U—Urticaria
D—Allergic Dermatitis
A—Asthma
RF—Rheumatic Fever
MS—Multiple Sclerosis
M—Migraine
o—Propositus

Figure 1.



H—Hay Fever
U—Urticaria
D—Allergic Dermatitis
A—Asthma
RF—Rheumatic Fever
MS—Multiple Sclerosis
M—Migraine
o—Propositus

Figure 2.



H—Hay Fever
U—Urticaria
D—Allergic Dermatitis
A—Asthma
RF—Rheumatic Fever
MS—Multiple Sclerosis
M—Migraine
o—Propositus

Figure 3.

and the absence of demonstrated sensitivity to the bacillus. Also arguing against this possibility is the infrequency with which demyelination has been produced experimentally by the use of bacterial toxins.[29]

Lastly, it has been demonstrated by Cavelti[30,31] and others that addition of streptococci to various tissues (heart and kidney) so alters them that they may be used as autoimmunizing antigens and produce lesions in the corresponding organs. It is postulated that rheumatic fever itself may not be the result of hypersensitivity to a component of Streptococcusc bacillus, but autoimmunization to heart muscle protein as altered by Streptococcal infection. It is possible that in certain families, repeated Streptococcal infections might result in rheumatic fever in some siblings by the above mechanism; in others the infections might alter nervous tissue and initiate a process of autoimmunization to that substance. Finally, it is possible that Streptococcal infection could exaggerate a hypersensitivity response to some externally introduced antigen such as a food substance.

Summary and Conclusions

1. Personal and family histories of 280 multiple sclerosis patients were investigated for the presence of rheumatic fever and allergic disorders.

2. Rheumatic fever occurred in a sibling of 6.8% of multiple sclerosis patients, and in a member of the immediate family in 18% of the patients.

3. A positive family history of a major allergic disease occurred in 34.9% of multiple sclerosis patients.

4. The possible mechanisms of hypersensitivity by which rheumatic fever and multiple sclerosis might be related are discussed.

Acknowledgment: The author wishes to express his appreciation to the members of the Multiple Sclerosis Societies of Minneapolis and St. Paul, without whose cooperation this study would have been impossible.

425 E. 63rd St., Kansas City, Mo.

BIBLIGRAPHY

1. McAlpine, D., Compston, N.D., and Lumsden, C.E.: Multiple Sclerosis. *E & S Livingstone Ltd.*, Edinburgh and London, 1955, Ch. XII.
2. Jonez, H. D.: Multiple Sclerosis and Allergy

Management with Histamine Therapy. *Ann. Allergy,* 8, 44, 1950.

3. Ferraro, A.: Pathology of Demyelinating Diseases As an Allergic Reaction of the Brain. *Arch. Neurol. & Psychiat.,* 52, 553, Dec. 1944.
4. Ehrentheil, O. F., Shulman, M. H., and Alexander, L.: Role of Food Allergy in Multiple Sclerosis. *Neurology,* 2, 412, 1952.
5. Prigal, S. J.: Allergy and Multiple Sclerosis. *J. Allergy,* 72, 170, March 1956.
6. Van Bogaert, L.: Essai d'interpretation des manifestations nerveuses observées an cours de la vaccination, de la maladie serique et des maladies eruptives. *Rev. Neuorl.,* 1932, 2, 1-26.
7. McAlpine, D.: Douglas, Multiple Sclerosis, A Plea for a Fresh Outlook. *B.M.J.,* March 2, 1957, 1, 5017.
8. McCarty, M.: The Immunity Response in Rheumatic Fever, in Rheumatic Fever; Symposium, ed. Thomas, Lewis. *U. of Minn. Press,* 1952.
9. Rantz, L. A.: The Streptococcal Etiology of Rheumatic Fever. *Med. Clin., N. Am.,* 39, 339, March, 1955.
10. Aikawa, J. K.: Hypersensitivity and Rheumatic Fever. *Ann. Int. Med.,* 41, 576, Sept. 1954.
11. Schwentker, F. F.: Epidemiology of Rheumatic Fever, in Rheumatic Fever; Symposium, ed. by Thomas, Lewis, *U. of Minn. Press,* 1952, pp. 17 ff.
12. Kurland, L.: The Frequency and Geographic Distribution of Multiple Sclerosis as Indicated by Mortality Statistics and Morbidity Surveys in the United States and Canada. *Am. J. Hyg.,* 55, 457, 1952.
13. Read, F. E. M., Ciocco, A., and Taussig, J. B.: Frequency of Rheumatic Manifestations Among Siblings, Parents, Uncles, Aunts and Grandparents of Rheumatic and Control Patients. *Am. J. Hyg.,* 27, 719, 1938.
14. Wilson, M. G., and Schweitzer, M.: Pattern of Hereditary Susceptibility in Rheumatic Fever. *Circulation,* 10, 699, Oct. 1954.
15. MacKay, R. P.: The Familial Occurrence of Multiple Sclerosis and Its Implications. *Pros., Ass. Res. Nerv. Dis.,* 28, 150, 1950.
16. Pratt, R. T. C., Compston, N. D., and McAlpine, D.: The Familial Incidence of Disseminated Sclerosis and Its Significance. *Brain,* 74, 191, 1951.
17. Roy, S. B., Sturgis, G. P., and Massell, B. F.: Application of the Antistreoptolysin-O Titer in Evaluation of Joint Pains and the Diagnosis of Rheumatic Fever. *New Eng. J. Med.,* 254, 95, 19 Jan. 1956.
18. Kennedy, F.: Allergy and Its Effects on the Central Nervous System. *J. Nerv. & Ment. Dis.,* 88, 91, 1938.
19. Pardee, I.: Allergic Reactions in the Central Nervous System. *Arch. Neurol. & Psychiat.,* 39, 1360, 1938.
20. Davison, H.: Allergy of the Nervous System. *Quart. Rev. Allergy,* 5, 157, 1951.
21. Raskin, N.: Antibrain Antibodies in Multiple Sclerosis. *Arch. Neurol. & Psychiat.,* 73, 645, June 1955.
22. Steiner, G.: A Serologic Complement Fixation Test for Multiple Sclerosis. *Arch. Neurol. & Psychiat.,* 34, 466, 1935.
23. Frick, E.: Serologische Untersuchungen bei Multipler Sklerose. *Deutsche Ztschr. Nervenh.,* 166, 54, 1951.
24. Rittwagen, M., Romano, F. J., and Svigals, M. P.: A Study of the Incidence of Allergy in Children with Rheumatic Fever. *Arch. Ped.,* 63, 639, 1946.
25. Hösemann, Von Friedrich: Beitrag zur Frage allergischer Vorgange bei rheumatischen Gelenkerkrankungen im Kindersalter. *Mschr. Kinderh.,* 103, 471, 1955.
26. Perger, F.: Die Testung von Stoffen die einen fördernden Einfluh auf das Krankheitsgeschehen des rheumatischen Formen dreises und der Multiplen Sclerose ausuben können. *Wien. Klin. Wschr.,* 68, 304, April 13, 1956.
27. Perry, W. P., Hahn, E. O., and Rammelkamp, C. H.: Antibody Production and Its Relation to Rheumatic Fever. *Clin. Res. Proc.,* 1, 4, 1953.
28. Störtebecker, T. B.: Common Infections in Disseminated Sclerosis and Other Diseases of the Nervous System. *Acta Med. Scandinav.,* 140, 41, 1951.
29. Wolf, A.: A Review of Experimental Studies on the Etiology of the Human Demyelinating Diseases. *Proc. First Internat. Congress of Neuropathology,* Sept. 8-13, 1952.
30. Cavelti, P. A.: Autoimmunologic Oisease. *J. Allergy,* 26, 95, 1955.
31. Raffel, S.: Immunity, Hypersensitivity, Serology. N. Y., 1953, *Appleton-Century-Crofts, Inc.,* Chap. 31.

Author's present address: Division of Neurology, University of Kansas Medical School, Kansas City, Kansas.

Drug Delirium Due to Meprobamate

(A Case Report)

HARRY F. DARLING, M.D.

This patient had had seven short term admissions in various psychiatric hospitals prior to September 1957. In 1952 she was diagnosed barbiturate addiction without psychosis on her first admission. She had been taking barbiturates for two years prior to this admission, increasingly so following several operations and the development of an arthritis which was later diagnosed as Marie-Strumpell disease. Psychiatric hospitalization was not necessary again until late in 1955 and by the middle of 1956 she had had six more admissions, on one occasion being diagnosed psychoneurotic and on the others variously as personality disorder—alcoholism, and delirium tremens. Her propensity to use drugs and alcohol was at least aggravated by the Marie-Strumpell disease.

For more than a year prior to the 1957 admission patient had been an active member of Alcoholics Anonymous. Five months prior to admission she had been started on 1600 mg. of meprobamate (Equanil) daily but soon was taking 8000 mg. daily. She entered Danvers State Hospital voluntarily. On the night of her admission and the day following she had severe grand mal type convulsions and went into status, which was relieved by appropriate medication. There was no epileptic history and the patient had not had convulsions on prior admissions. She was confused, had transient orientation and memory defects, but at times her sensorium was clear; she had visual hallucinations, thinking that insects were running about the ward and that there were men on the walls. On the fourth day the patient was completely without psychosis and on the sixth day left against advice. Statements from her family and an alcoholic clinic she attended regularly in Boston denied the use of alcohol. She was not hospitalized long enough for electroencephalography.

From Danvers State Hospital, Hathorne, Mass.

Summary

This patient had been using meprobamate in doses of 8000 mg. daily, as a substitute, apparently, for alcohol, while working as a very active member of Alcoholics Anonymous. Despite the astronomic dose it took several months for her to develop an acute brain syndrome, which lasted only three days.

BOOK REVIEWS

A SEARCH FOR MAN'S SANITY. The Selected Letters of Trigant Burrow. Oxford Press. 592 p. 18.75.

This volume consists of a series of letters from the writings of Dr. Burrow, fifteen chapters of them with a biographic text which either introduces or is incorporated into each chapter. The editors have, wherever possible, let the letters tell the story of Dr. Burrow's turbulent but interesting life. He was a prodigious letter writer and his epistles apparently went through the world to colleagues and opponents, to the great, the near great and the ordinary.

Anyone acquainted with Dr. Burrow's scientific productions will remember that many of them were prolix, ponderous and difficult for the uninitiated to understand. However, his letters are different. Many of them, as Sir Herbert Read says, demonstrate that "his epistolary style was a model of clarity and even rose to eloquence." In them he "had surely modified his scientific rigor and come out to meet our lay incapacities."

One of the men who early brought psychoanalysis to this country, he deviated after a few years of practice, though he continued to maintain his allegiance. His interest shifted to group analysis and he and some of his students broke with their colleagues and began an intensive scrutiny of each others' motivations. In order to further this work, the Lifwynn Foundation was started in 1927 and, as the work progressed, new concepts of a physiological nature were incorporated into the thinking of the group.

Admittedly, there is poetry in these letters; romance, too, for his relationship with his bride-to-be is chronicled—yet, there is something frustrating in the volume. One would like to know about the other end of the correspondence. What did the recipients of these letters think and write? Who initiated the correspondence? What did Freud actually say, and why? While it probably would have been a prodigious task for the editors, the book might have gained had some of the less important of the letters been omitted and the correspondence of those important to the doctor been included in full.

F. J. Braceland, M.D., Ss.D.

ESSENTIALS OF CLINICAL NEUROANATOMY AND NEUROPHYSIOLOGY by John T. Manter, Ph.D., M.D. Published by F. A. Davis Company, 1914-16 Cherry Street, Philadelphia 3, Pa.

The author has fulfilled in this monograph his object, providing a short but comprehensive survey of the human Central Nervous System. This title "Essentials of Clinical Neuroanatomy and Neurophysiology" appears ambiguous since—(1) new facets of the neurological sciences are unfolding constantly—(2) the integration of structural (anatomic) with functional (physiologic) relationships are often not clear enough to formulate clinically a focal diagnosis.

However, the sequence of the chapter division permits the reader to review and to relearn neurology easily especially since clear diagrams and/or drawings facilitate comprehension and localization of the subject matter. Chapters 8, 13, 14 and 21 are especially instructive.

Dr. Manter's monograph is the neurologiv handbook for physicians in the practice of medicine. It can be recommended to students of medicine and psychology.

One page with specific reference to the literature (i.e., Chapter 3 or 20) will enrich this practical booklet. A firmer cover is recommended.

Dr. Hans H. Reese, M.D.
Professor of Neurology and Psychiatry
University of Wisconsin, Madison, Wis.

A NEUROPSYCHIATRIC FOUNDATION
THE

ROGERS MEMORIAL HOSPITAL

The Hospital is situated on the Nashotah Lakes, 30 miles west of Milwaukee, providing the ideal, restful country environment and the facilities for the modern methods of therapy of psychoneuroses, psychosomatic disorders, alcoholism, and the other neurologic and psychiatric problems. Occupational therapy and recreational activities directed by trained personnel.

OCONOMOWOC, WISCONSIN
PHONE LOGAN 7-5535

EUGENE FRANK, M.D.
WILLIAM C. JANSSEN
LOREN J. DRISCOLL, M.D.

OWEN OTTO, M.D.
Medical Director

LEROY A. WAUCK, PH.D.
Clinical Psychologist
JOSEF A. KINDWALL, M.D.
Consultant

FAIR OAKS
INCORPORATED
SUMMIT, NEW JERSEY

A fully approved Hospital for intensive treatment and management of problems in Neuropsychiatry.

OSCAR ROZETT, M.D.
Medical Director

THOMAS P. PROUT, JR.
Administrator

BEVERLY HILLS CLINIC and SANITARIUM

210 N. Westmoreland Avenue WHitehall 3-4651
Dallas 11, Texas

A private clinic and hospital for nervous and mental diseases both for in-patients and out-patients—stressing a homelike environment with separate building units and special cottages—air-conditioned.

A complete neuropsychiatric diagnostic and treatment center including a department of psychology—encephalography—clinical laboratory and X-ray—psychotherapy—electroshock and insulin coma therapy, as well as psycho-surgery.

ARTHUR J. SCHWENKENBERG, M.D.
JOSEPH L. KNAPP, M.D.
JACKSON H. SPEEGLE, M.D.
Neurology

FRED H. JORDAN, M.D.
HENRY P. HARE, JR., M.D.
LUDLOW M. PENCE, M.D.
Psychiatry